

# **EXHIBIT 77b**

Document title: (2) Adrian H on X: "@DanClintonRN @pash22 @ProfRobHoward @LogarithmicDis @LonSchneiderMD @MadhavThambiset @RenegadeSynapse @nvillain\_alz @CorriveauNick @DavidJonesBrain @MemoryDoc @ajlees @PhilAlz @DrTFfromKC @smead2 @AlbertoEspay @Kariem\_Ezzat @seb\_walsh @EWidera @KasperKepp @Jennife10651535 @eturnermd1 @VincentPlanche @ayton\_scott @macesari @schrag\_matthew @HHS\_ORI @FDACDERDirector @CassavaSciences @CUNY @KatherineMLewin @ClicksAndHisses @NIH @adamfeuerstein It's a totally different issue, but I can assure you that many of those outraged with \$SAVA were also outraged with Aduhelm and FDA shenanigans and skeptical of amyloid Abs. But there's equivalence between that and allegedly completely fake science and an allegedly imaginary drug" / X

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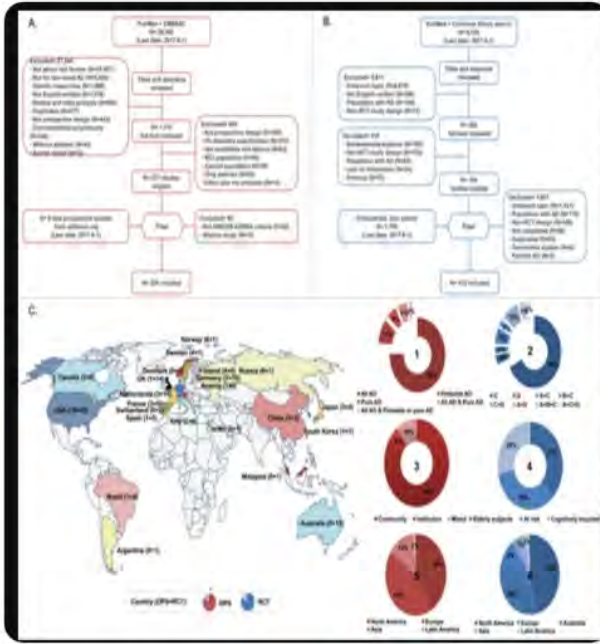
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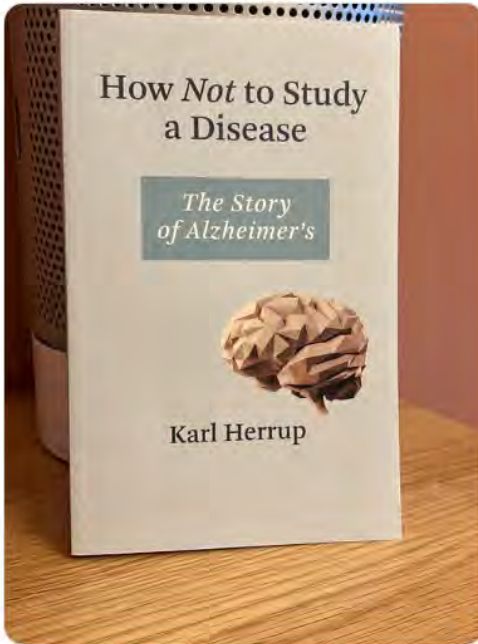


1 1 3 1K



**Jamie Timmons** @metapredict · Apr 24, 2023  
Any that worked? (real worked, replicated worked, not marketing worked?)... tricky to advise people to take preventative steps (same bs in Cardiovascular where Exercise doesn't reduce hard CV endpoints)

Looking forward to reading my new book (Wellcome Trust book store) !



3 7 1.1K



**Seb Walsh** @seb\_walsh · Apr 24, 2023  
No.

P.S. it's a great book

2 2 2K



**Jan**  
@810964733763B

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@Adrian\_H

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**Ash Paul**  
@pash22

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**philip robinson** @pxrobbo · Apr 25, 2023  
Who's got the glove?

1

2

810

**Ash Paul** @pash22 · Apr 25, 2023  
Won't it be Madhav? He mooted the challenge, so presumably he has slapped Rob across his face with the empty glove.

1

3

844

**David Rind** @dmrind · Apr 25, 2023  
I picture Madhav as more of a metal gauntlet kind of guy.

1

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886

**Robert Howard** @ProfRobHoward · Apr 25, 2023  
I'm running away, anyway. Fast.

1

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928

**Jason Cohen** @MemoryDoc · Apr 25, 2023  
But think of the research we could fund by selling tickets!

1

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963

**Madhav Thambisetty** @MadhavThambiset · Apr 25, 2023  
Federal regulations expressly prohibit me from \*ahem\* free-lancing

2

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**Robert Howard** @ProfRobHoward · Apr 25, 2023  
We should stick to squabbling over the contents of pizza boxes.

2

5

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**Ash Paul** @pash22 · Apr 26, 2023  
That's a bit rich Michelle, criticising a person who has spent his entire medical career in psychiatry looking after dementia patients and who was one of the the principal investigators of the pioneering AD2000 trial.

1

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1.2K

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**Ash Paul** @pash22 · Apr 26, 2023  
Sure you are. It's just that 'opinion' is not always right. I'm NOT saying your opinion is wrong.  
[evidentlycochrane.net/expert-opinion...](https://evidentlycochrane.net/expert-opinion...) via @Prof @martinjburton and @CochraneUK

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@810964733763B

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**Adrian H** @Adrian\_H  
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From evidentlycochrane.net

1 907

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**Ash Paul** @pash22 · Apr 26, 2023  
Rob has spent 735 yrs plus in looking after dementia patients and he is a highly acknowledged academic globally. I'm sure he is entitled to his opinions, just as you and I are. Moreover, Rob has a v dry/cynical sense of humour which some ppl take very seriously but shouldn't IMO.

3 4 1K

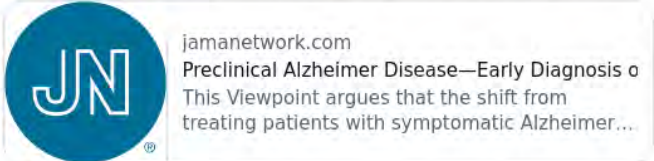
**Ivana Fulli** @DrFulli · Apr 29, 2023  
I am afraid prof. Howard is accused of inventing the unfortunate people with normal « wrinkles on their brain » misdiagnosed with dementia.

1 1 921

**Ivana Fulli** @DrFulli · Apr 29, 2023  
It seems urgent to alert about overdiagnosis when Pharma targets early dementia diagnosis as market for Rx with dangerous adverse-effects.

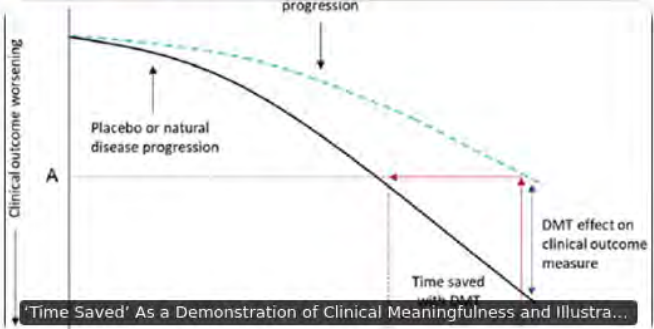
1 903

**Ash Paul** @pash22 · Apr 29, 2023  
There was a v gud 2019 article in @JAMAInternalMed by @UMich researchers  
"Preclinical Alzheimer Disease: early Diagnosis or Overdiagnosis"



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**Ash Paul** @pash22 · Apr 30, 2023  
'Time Saved' As a Demonstration of Clinical Meaningfulness and Illustrated Using the Donanemab TRAILBLAZER-ALZ Study Findings  
[link.springer.com/article/10.142...](https://link.springer.com/article/10.142...) via @WesselsAlette et al  
@LonSchneiderMD @barttels2



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From link.springer.com

**Ash Paul** @pash22 · May 3, 2023

@LillyPad 's Alzheimer's therapy Donanemab slowed patients' rate of cognitive decline, data show [investor.lilly.com/news-releases/...](https://investor.lilly.com/news-releases/) via @matthewherper & @adamfeuerstein

investor.lilly.com  
Lilly's Donanemab Significantly Slowed Cognitive  
The Investor Relations website contains information about Eli Lilly and Company's ...

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**Ash Paul** @pash22 · May 3, 2023

@LillyPad 's Alzheimer's drug donanemab slows cognitive decline by 35% in PhIII, setting up showdown with Eisai's Leqembi [endpts.com/lilys-alzheim...](https://endpts.com/lilys-alzheim...) via @RLCscienceboss

Lilly's Alzheimer's drug donanemab slows cognitive decline by 35% in P...  
ENDPOINTS NEWS

From endpts.com

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**Seb Walsh** @seb\_walsh · May 3, 2023

Copy and paste all the hype and expected responses from expected responders from aducanumab and lecanemab (and the vested interests)

Copy and paste all the critics' concerns about aducanumab and lecanemab

**Seb Walsh** @seb\_walsh · May 3, 2023

Press release on #donanemab phase III trial.

No absolute effects ... wonder why!? But, based on the relative changes, slowing in rate of decline is comparable to lecanemab.

...

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**Robert Howard** @ProfRobHoward · May 3, 2023

Yup.

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**Ash Paul** @pash22 · May 4, 2023

World 'on cusp of first generation of treatments for Alzheimer's' as new drug 'slows symptoms': New drug donanemab appears to slow

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**Adrian H** @Adrian\_H

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Ash Paul @pash22 · May 4, 2023

World 'on cusp of first generation of treatments for Alzheimer's' as new drug 'slows symptoms': New drug donanemab appears to slow decline associated with Alzheimer's  
[Independent.co.uk/news/health/al...](#) via @janekirbyPA



World 'on cusp of first generation of treatments for Alzheimer's' as new ...

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Ash Paul @pash22 · May 5, 2023

Simple inexpensive tests found to predict dementia risk years in advance: 'Incorporating muscle function tests as part of dementia screening could be useful to identify high-risk individuals', says @marc\_p\_sim et al study  
[Independent.co.uk/news/science/t...](#) via @Social3uScience



Simple tests may help predict dementia risk years in advance

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Ash Paul @pash22 · May 7, 2023

A chance to beat back Alzheimer's, and we're not ready in UK  
[thetimes.co.uk/article/5e800c...](#) via @Ben\_Spencer

thetimes.co.uk  
The Times & The Sunday Times  
News and opinion from The Times & The Sunday Times

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Ash Paul @pash22 · May 7, 2023

New Eli Lilly Alzheimer's data poses @MedicareGov coverage conundrum  
[statnews.com/2023/05/04/lil...](#) via @rachelcohrrs



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New Eli Lilly Alzheimer's data poses Medicare coverage conundrum

From statnews.com

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**Ash Paul** @pash22 · May 8, 2023  
Access to New Alzheimer's Drugs Might Depend on Where You Live in USA: Big clinics are giving Leqembi to some patients while rural providers wait and watch  
[wsj.com/articles/acces...](#) via @dmossbergen et al



Access to New Alzheimer's Drugs Might Depend on Where You Live

From wsj.com


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**Ash Paul** @pash22 · May 8, 2023  
'Part of you dies as well': the toll of caring for loved ones with dementia [theguardian.com/society/2023/m...](#) via @byameliahill @Jennife10651535 @barttels2



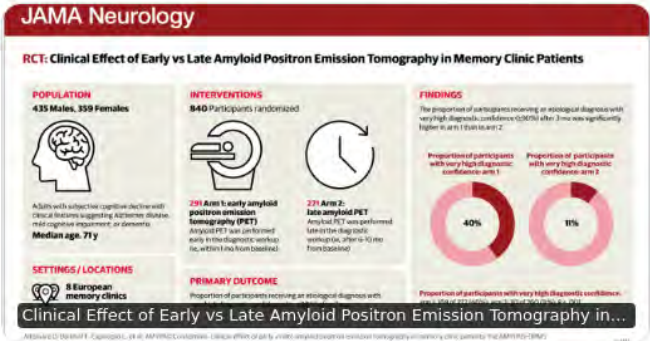
theguardian.com  
'Part of you dies as well': the toll of caring for lo  
A new drug could slow the pace of Alzheimer's.  
Three people with experience of the disease ...

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**Ash Paul** @pash22 · May 8, 2023  
Clinical Effect of Early vs Late Amyloid Positron Emission Tomography in Memory Clinic Patients: The AMYPAD-DPMS RCT  
[jamanetwork.com/journals/jaman...](#) via @GiovanniFrisoni et al




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From jamanetwork.com

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**Ash Paul** @pash22 · May 15, 2023

Colombian man's genetics should have doomed him to Alzheimer's: Instead, a rare mutation offers clue to protection  
[endpts.com/colombia-mans-...](https://endpts.com/colombia-mans-...) via @RLCscienceboss



From endpts.com

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**Nicolas Villain** @nvillain\_alz · May 15, 2023

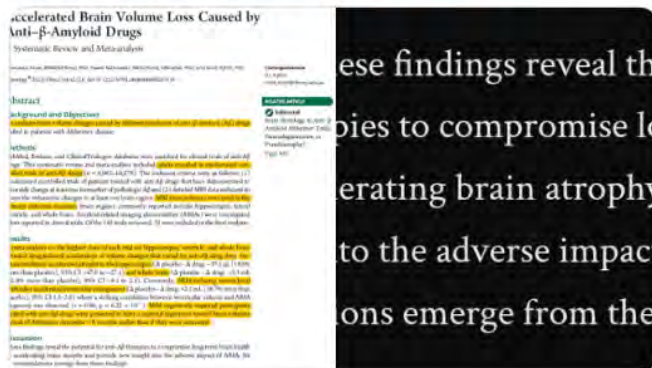
nature.com

Resilience to autosomal dominant Alzheimer's d  
 Nature Medicine - Case report of an individual  
 heterozygous for a rare RELN-COLBOS variant...

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**Ash Paul** @pash22 · May 16, 2023

Accelerated Brain Volume Loss Caused by Anti- $\beta$ -Amyloid Drugs: A Systematic Review and Meta-analysis  
[n.neurology.org/content/100/20...](https://n.neurology.org/content/100/20...) via @ayton\_scott et al



3 5 1.4K

**Philip Robinson** @pxrobbo · May 16, 2023

Why isn't this open access?

2 1 1.1K

**Jennifer Richards** @jennife10651535 · May 16, 2023

As an ex medical librarian:  
 most journals require subscriptions, which is frustrating I know. We used to operate an interlibrary loan system. I'm not sure how they

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@amsterdamunc 's # WillemVanGool abt lack of sensitivity analysis to assess for bias from unbinding in #Lecanemab trial

**Madhav Thambisetty** @MadhavThambiset · May 19, 2023

Much more blunt than our commentary here [pubmed.ncbi.nlm.nih.gov/36609712/](https://pubmed.ncbi.nlm.nih.gov/36609712/) where we emphasized that the lack of any sensitivity analyses to unblinding from infusion reactions in the #lecanemab trial is a major concern @ProfRobHoward @pash22

LETTER TO THE EDITOR

Unblinding in the lecanemab trial in Alzheimer's disease

Willem A. Van Gool

Outright breaking of the masked treatment allocation in a substantial proportion of lecanemab treated participants is almost certain. This is problematic especially since the primary outcome and most of the secondary outcomes require input of a caregivers, who were partly unblinded. Before any claim of a 'clear clinical benefit' of lecanemab can be accepted and before trying to answer hard questions like 'why has it taken so long and what is next', post-hoc analyses are warranted with stratification for the occurrence of infusion reactions. My prediction would be that trial participants with infusion reactions, both in the lecanemab as well in the placebo group, fare about 25% better than those without.

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**Ash Paul** @pash22 · May 25, 2023

Case Study Reveals Potentially Lethal Side Effects of Lecanemab for Treatment of Alzheimer's Disease [j-alz.com/content/case-s...](https://j-alz.com/content/case-s...) via @journal\_ad

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**Ash Paul** @pash22 · May 25, 2023

The full article is here "Neuropathology of Anti-Amyloid-β Immunotherapy: A Case Report" [content.iospress.com/articles/journ...](https://content.iospress.com/articles/journ...) via @PJamshidi\_MD et al

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**Ash Paul** @pash22 · Jun 2, 2023

US @MedicareGov holds firm on Alzheimer's drug coverage policy [statnews.com/2023/06/01/med...](https://statnews.com/2023/06/01/med...) via @rachelcohers



From statnews.com

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**Dave Weisman** @dcweisman · Jun 2, 2023

So far they seem to have only enough courage to discriminate against ALzheimer's.

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So far they seem to have only enough courage to discriminate against Alzheimer's.

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Ash Paul @pash22 · Jun 17, 2023  
Prof @AlbertoEspay et al are petitioning @US\_FDA NOT to approve Lecanemab  
[twitter.com/AlbertoEspay/s...](https://twitter.com/AlbertoEspay/s...)  
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Ash Paul @pash22 · Jun 17, 2023  
In addition, Prof @jasonkarlawish has written in @statnews abt the urgent need for @US\_FDA & @CMSSGov to work together on a 'Risk Mitigation' scheme for Lecanemab

Jason Karlawish @jasonkarlawish · Jun 17, 2023  
The FDA needs a risk evaluation and mitigation strategy for #Alzheimer's drug lecanemab [statnews.com/2023/06/16/the...](https://statnews.com/2023/06/16/the...)  
@statnews The problem isn't the drugs; it's the drugs in the system. @US\_FDA & @CMSSGov should collaborate to move these Rx into practice. @pash22 @ProfRobHoward

Kasper Planeta Kepp @KasperKepp · Jun 18, 2023  
I wonder how those who seem to trust the lecanemab trial as proof of effect explain that the drug works so much better in >75y than in <65y. Goes a bit against the common claim that the drug should be applied early to have effect.

(B) Other Factors

	No. of Participants (placebo, lecanemab)	Adjusted Mean Difference	Percent Biasing of Decline (%)
Overall	875, 888	-0.65	27
ApoE4 Genotype Status			
Noncarrier	275, 287	-0.75	41
Heterozygote	448, 456	-0.50	30
Homozygote	152, 156	0.28	-22
Sex			
Female	484, 443	-0.29	12
Male	411, 416	-0.71	43
Age			
<65	178, 168	-0.08	6
65-74	381, 368	-0.37	23
≥75	316, 325	-0.72	40

Ash Paul @pash22 · Jun 18, 2023  
Interesting observations by Kasper @KasperKepp & Dan @DanClintonRN in this separate twitter thread

Kasper Planeta Kepp @KasperKepp · Jun 18, 2023  
Replying to @jasonkarlawish @statnews and 4 others  
There are 3 papers (Lansdall, Andrews, Wessels) that set the clinical meaningful threshold >1 for CDR-SB - (none of them cited by Van Dyck et al.).  
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CDR-SB change	Total	Female	Male	EUR	US	<65y	>75y	MCID
Effect, diff CDR-SB	0.45	0.20	0.73	0.33	0.52	0.08	0.72	1
Effect, absolute %	2.5	1.1	4.1	1.8	2.9	0.4	4.0	5.5
"Effect", ratio %	27	12	43	14	34	6	40	?

Relevant people

Adrian H @Adrian\_H  
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Dan Clinton - The Av @DanClintonRN  
Nurse, Tutor, Author. Believer in good definitions, the scientific method, & comparing benefits & harms in like terms. Seeking to prevent iatrogenic harm.

Ash Paul @pash22  
Public Hlth Dr, interested in evid-based health services commissioning, clinical leadership & hlth policy. My views are my own, RTs are no endorsements

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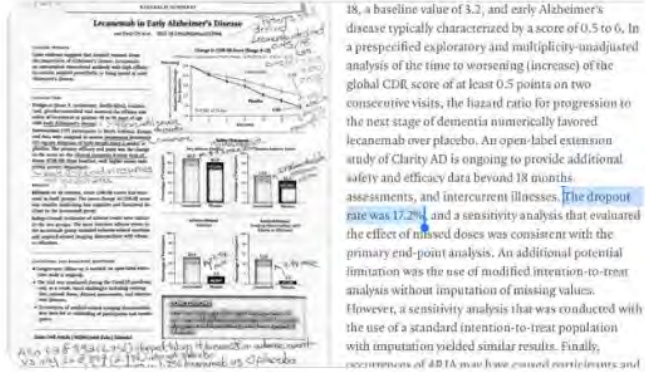
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Effect, diff CDR-SB	0.45	0.20	0.73	0.33	0.52	0.08	0.72	1
Effect, absolute %	2.5	1.1	4.1	1.8	2.9	0.4	4.0	5.5
"Effect", ratio %	27	12	43	14	34	6	40	?

3 1 5 1.5K



**Dan Clinton - The Awesome Nursin** @DanClint · Jun 18, 2023 ...  
Lecanemab: 1) didn't improve cognition 2) in 1 manufacturer funded, designed, and processed study slowed decline 2.5% 3) requires q 2 week IV infusions 4) destroys 1.2% of brains 5) costs \$26,500/yr 6) causes rxn in > 25% 7) 17.2% dropout rate 8) 6.9% stopped d/t adverse rxns



1 1 3 936



**Ash Paul** @pash22 · Jun 20, 2023 ...  
The @AlzDisInt 's position statement regarding @US\_FDA 's pending approval of lecanemab.



2 2 5 1.4K



**Nicolas Villain** @nvillain\_alz · Jun 20, 2023 ...  
Thx Ash!  
Are the Alzheimer International Society and Alzheimer Disease International the same entity?

1 865



**Ash Paul** @pash22 · Jun 20, 2023 ...  
Nope Nicolas. Alz Int Society is @ALZINT1

1 891



**Nicolas Villain** @nvillain\_alz · Jun 20, 2023 ...  
Ok, that's what I thought. So it was just the wrong identification in your first Tweet

1 918



**Ash Paul** @pash22 · Jun 20, 2023 ...  
Oops, v sorry for the typo Nicolas

1 933

Jan  
@810964733763B

## Relevant people



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@Adrian\_H

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**Ash Paul** @pash22 · Jun 20, 2023  
Oops, v sorry for the typo Nicolas

1 2 933

**Ash Paul** @pash22 · Jun 20, 2023  
I will repost my erroneous tweet viz @ALZINT1 (NOT @AlzDisint )'s position statement on the pending approval of Lecanemab by @US\_FDA

2 5 1.1K

**Robert Howard** @ProfRobHoward · Jun 20, 2023  
I made the same mistake, Ash. Crafty to make themselves look like ADI!

1 3 1.1K

**Ash Paul** @pash22 · Jun 23, 2023  
More on the Lecanemab analysis by Alberto @AlbertoEspay & @Matthew @schrag\_matthew

**Alberto J Espay** @AlbertoEspay · Jun 23, 2023  
There is no lecanemab "improvement" but a little less worsening, by -1.21 with lecanemab, -1.66 with placebo. The 0.45 difference is below what can be perceived (1-2 points). There is no "27% improvement" but a puny 2.5% slower decline. @schrag\_matthew ...  
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2 11 7.6K

**Ash Paul** @pash22 · Jun 30, 2023  
Chk out @waynestate 's #MarkkuKurkinen 's blog 'What's Leqembi got to do with Alzheimer's dementia?'

**Kasper Planeta Kepp** @KasperKepp · Jun 30, 2023  
Replying to @KasperKepp  
See also this blog post on lecanemab by Markku Kurkinen in @journal\_ad  
[j-alz.com/editors-blog/p...](http://j-alz.com/editors-blog/p...)

1 4 2K

**Ash Paul** @pash22 · Jul 1, 2023  
Alberto @AlbertoEspay 's message to @US\_FDA & @alzassociation on Lecanemab

**Alberto J Espay** @AlbertoEspay · Jul 1, 2023  
Important thread by @KasperKepp, one of the authors of the "Lecanemab is neither safe nor effective" letter ([chn9.it/yqxbK6PHYV](http://chn9.it/yqxbK6PHYV)), which has accrued 420 signatures. How do we let the @US\_FDA and @alzassociation know that a "consensus" around #lecanemab is an illusion?

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**Adrian H** @Adrian\_H  
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1 6 2.4K

Ash Paul @pash22 · Jul 5, 2023  
@RxRegA makes pertinent comments abt @US\_FDA 's recent bizarre ads

Jessica Adams @RxRegA · Jul 4, 2023

Is there an FDA-approved drug to maintain mental function in Alzheimer's? I see this tweet from FDA (pic) and did a double take to ask this question. Where I'm coming from I know the recent beta-amyloid drugs are still pending clinical outcomes. I thought at most you could say...  
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FDA U.S. FDA @US\_FDA · Jun 30

Although there is no cure, several FDA-approved medications are available to help people maintain mental function and slow or delay the symptoms of Alzheimer's disease.  
[Learn more at bit.ly/3Plo3Kb](#)  
[#AlzheimersAwareness](#)  
[#ENDALZ](#)

You may be at a higher risk of developing ALZHEIMER'S DISEASE if you:

Are over age 60

Are a woman

Engage in few physical, mental, or social activities

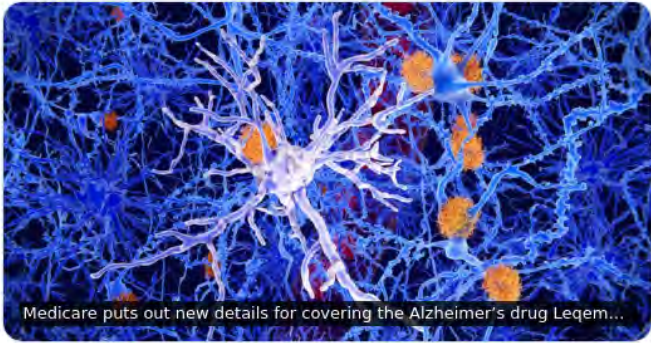
Have a family history of Alzheimer's disease

Have heart disease or an associated condition

Had a moderate or severe head injury

2 5 2.4K

Ash Paul @pash22 · Jul 6, 2023  
@MedicareGov puts out new details for covering the Alzheimer's drug Leqembi, as the US health system readies for potential approval today  
[statnews.com/2023/06/22/med...](#) via @rachelcohrs . Lon @LonSchneiderMD & Sam @samgandy are quoted in this article

  
Medicare puts out new details for covering the Alzheimer's drug Leqem...

From statnews.com

1 5 1.7K

Ash Paul @pash22 · Jul 6, 2023  
@US\_FDA approves first Alzheimer's therapy shown to clearly slow cognitive decline [statnews.com/2023/07/06/leq...](#) via @adamfeuerstein & @damiangarde

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@US\_FDA approves first Alzheimer's therapy shown to clearly slow cognitive decline [statnews.com/2023/07/06/leq...](https://www.statnews.com/2023/07/06/leq...) via @adamfeuerstein & @damiangarde

From statnews.com

2

4

4

2.2K

**Lon S. Schneider, MD** @LonSchneiderMD · Jul 6, 2023  
@statnews hardly mentions the new restricted indication, contraindication, & Black Box Warning. They continue to hype a 27% relative change (which is not a statistic) rather than the actual -0.45 CDR-SB statistical difference, or the real 8% absolute difference from placebo.

6

8

30

13K

**David Rind** @dmrind · Jul 8, 2023  
Serious question: what do you think 27% is in this trial if it's not a statistic?

3

1

1.2K

**Lon S. Schneider, MD** @LonSchneiderMD · Jul 9, 2023  
Serious response: a statistic summarizes part of a sample &/or is used in model for hypothesis testing. IMO u cn say '27% difference from -1.66' pts bec it's same as -0.45 the mean diff statistic that was tested. To use naked '27%' misleads & misinforms. This is not quibbling.

5

5

18

5.6K

**David Rind** @dmrind · Jul 9, 2023  
Okay. As mentioned, I wasn't trying to get into a RRR vs. ARR debate: each statistic has its merits in answering certain questions. However, to my mind both are clearly statistics.

1

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757

**Nicolas Villain** @nvillain\_alz · Jul 9, 2023  
I beg to differ on this one, @dmrind: you don't perform statistics from percentages of evolution in each participant of these studies . RRR are just posterior calculations to put the ARR main result into perspective; so, not a stat per se.

**Nicolas Villain** @nvillain\_alz · Jul 9, 2023  
Replying to @LonSchneiderMD @dmrind and 47 others  
Can't agree more with Lon! We never perform stats on RRR but on ARR because of the non-normal distribution of percentages. So, RRR is simply used to ease the interpretation of the ARR since most readers don't know the scale. Like always, ...  
[Show more](#)

2

1

1.2K

**David Rind** @dmrind · Jul 9, 2023  
The risk in a treated population is a parameter as is the risk in an untreated population. Statistics can estimate both of these risks for

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**Adrian H** @Adrian\_H  
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1.2K

David Rind

@dmrind · Jul 9, 2023

The risk in a treated population is a parameter as is the risk in an untreated population. Statistics can estimate both of those risks for a sample and can estimate both the ARR and the RRR. All four of these are considered statistics in my world. Your mileage may vary.

1

2

789

Nicolas Villain

@nvillain\_alz · Jul 9, 2023

We may differ on semantics here. Any statistical test (what I call statistics) performed on RCT outcomes is based on ARR, not RRR. Of course, comparing the mean of your outcome to the evolution of the placebo group and making a ratio is maths from RCT parameters; but is it stat?

1

3

855

Madhav Thambisetty

@MadhavThambiset · Jul 9, 2023

And what makes this "math" particularly devious is that it creates the marketing slogan and jingle for the drug. Patients believe the Rx "slows the disease by 27%" which it absolutely does not. It's a cynical, misleading ploy that preys on patient's hopes.

1

4

5

4.9K

Dave Weisman

@dcweisman · Jul 9, 2023

Slowing the disease by 27% is exactly the right way to phrase a study who's primary outcome was "change from baseline in the CDR-SB at 18 Months" and showed a 27% difference in CDR-SB at 18 months.

1

1

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672

Madhav Thambisetty

@MadhavThambiset · Jul 9, 2023

See [ajtrev.substack.com/p/no-i-dont-be...](https://ajtrev.substack.com/p/no-i-dont-be...) & [academic.oup.com/braincomms/art...](https://academic.oup.com/braincomms/art...) & [tinyurl.com/mwzp35dc](https://tinyurl.com/mwzp35dc) It is a "27% difference from 1.66 CDRSB points" which does not mean "27% slowing in #Alzheimers" which is what the headline seems to be

1

2

5

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@810964733763B

Ash Paul

@pash22 · Jul 11, 2023

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benefits of drug treatment, especially for lay audiences.

1 2 5 1K

Ash Paul

@pash22 · Jul 11, 2023

@BernieSanders


 wants 

@HHSGov

 to look into the price of Eisai's newly approved Alzheimer's drug [endpts.com/bernie-sanders...](https://endpts.com/bernie-sanders...) via 

@ZacharyBrennan

ENDPOINTSNEWS



Bernie Sanders wants HHS to look into the price of Eisai's newly approv...

From endpts.com

1 2 723

Ash Paul

@pash22 · Jul 11, 2023

Very good editorial in 

@bmj\_latest

 by 

@iqwig

 's 

#BeateWieselar

 which resonates very well with the recent 

@US\_FDA

 approval of Lecanemab

"Patients need better treatments, not just more of the same"

bmj.com

Patients need better treatments, not just more c

Drug regulation and development must be aligned with clear public health goals A well ...

1 1 2 1K

Ash Paul

@pash22 · Jul 11, 2023

Lecanemab Registry Enrollment by 

@MedicareGov

 for Alzheimer's Drug Coverage Won't Help Much: A minimalist policy for a minimalist treatment [medpagetoday.com/opinion/second...](https://medpagetoday.com/opinion/second...) via 

@AlexChaitoff

 et al HT 

@barttels2

medpagetoday.com

Opinion | Registry Enrollment for Alzheimer's Dr

A minimalist policy for a minimalist treatment

1 2 5 1.4K


Ash Paul

@pash22 · Jul 12, 2023

How are US insurers handling the Alzheimer's drug Leqembi and related scans?

[statnews.com/2023/07/12/leq...](https://statnews.com/2023/07/12/leq...) via 

@rachelcohrrs



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How are insurers handling the Alzheimer's drug Leqembi and related sc...

From statnews.com

1 2 763



Ash Paul @pash22 · Jul 14, 2023

Great tweetorial on the new Alz' drugs by Eric @EWidera



Eric Widera, MD @EWidera · Jul 13, 2023

Biogen was hoping to make history with Aduhelm as one of the "the top pharmaceutical launches of all time. It didnt. It was possibly one of the worst launches of all time. The Aduhelm files tells us a lot though about how drug prices are set and some of them may surprise you....

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Our ambition is to make history



Our ambitious patient goals for 2021 and beyond will establish ADUHELM as one of the top pharmaceutical launches of all time

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Ash Paul @pash22 · Jul 14, 2023

@US FDA Approval of Lecanemab for Alzheimer's: Alz' Experts including @ProfRobHoward Weigh In [medscape.com/viewarticle/99...](https://www.medscape.com/viewarticle/99...) via @youmshajekian



medscape.com

FDA Approval of Lecanemab for Alzheimer's: Exp  
Last week's FDA approval of the anti-amyloid lecanemab is being hailed by some Alzheimer...

2 1 6 864



Ash Paul @pash22 · Jul 15, 2023

With momentum on Alzheimer's therapies, Europe sees delivery challenges ahead, too  
[statnews.com/2023/07/14/alz...](https://www.statnews.com/2023/07/14/alz...) via @DrewQJoseph



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With momentum on Alzheimer's therapies, Europe sees delivery challen...

From statnews.com

**Ash Paul** @pash22 · Jul 16, 2023  
Delirium, blood biomarkers for neurodegeneration, and dementia  
[thelancet.com/journals/lanhl...](https://thelancet.com/journals/lanhl...) via @VincentPlanche



2 1 3 890

**Ash Paul** @pash22 · Jul 16, 2023  
This is an extraordinary tweet from Nicolas @nvillain\_alz which raises hugely important issues

**Nicolas Villain** @nvillain\_alz · Jul 16, 2023  
With the confirmation that the NIA wants to switch from a clinical to a biological definition of AD: I have an honest question. We will increase the nb of cases by 5-10 times or more, including numerous who will die without symptoms. Is AD still a major public health issue? #AAIC



1 4 1.1K

**LogarithmicDis** @LogarithmicDis · Jul 16, 2023  
Few ppl are willing to address the effects of early diagnosis by biomarkers alone would have on patients emotional life and insurance (health and life) -

When many will not develop clinical symptoms, ever.

3 727

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**Ryan Townley** @DrTFromKC · Jul 16, 2023  
Years of deliberation with 7 months of intense meetings between over 30 experts in the field with a separate advisory board of other experts in the field.

3 5 829

**Ash Paul** @pash22 · Jul 17, 2023

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**Ash Paul** @pash22 · Jul 17, 2023  
Hi Ryan, IMO, u need to openly declare that you have a huge intellectual Col (NOT financial Col), because u do pioneering research on relationship of fasting glucose and longitudinal Alzheimer's disease imaging markers  
[alz-journals.onlinelibrary.wiley.com/doi/full/10.10...](https://alz-journals.onlinelibrary.wiley.com/doi/full/10.10...)

Dysregulation of glucose in late life may signal preclinical brain change prior to clinically relevant cognitive decline. Additional work is needed to determine whether treatments specifically targeting fasting glucose levels may impact change in brain structure or cerebral amyloid in older adults.

**Trey Bateman** @RenegadeSynapse · Jul 17, 2023  
Nearly everyone on this thread has substantial intellectual COI. I'm not sure Ryan's middle author paper on fasting glucose and AD biomarkers is his largest reason to have intellectual COI in this space lol

**Nicolas Villain** @nvillain\_alz · Jul 17, 2023  
I do! I'm the joint first author of the last IWG paper! My initial point about disclosures referred to the participation of numerous representatives of the industry and biomarker researchers in this expert group.

**Ryan Townley** @DrTFromKC · Jul 17, 2023  
I have similar concerns about NIA-AA COI.


Trey was merely commenting on Ash's very odd tweet.  
I'm still baffled by it tbh and I get lots of weird replies in here.


**Ash Paul** @pash22 · Jul 17, 2023  
I'm not sure why my comment was odd/bizarre Ryan & why Trey saw red with my tweet. U have now qualified urself by tweeting u too have concerns abt @NIHAging grup's Col. U did no such thing when u immediately replied 2 Gregg's tweet. Your immediate reply suggested 2 me ... 1/n


Years of deliberation with 7 months of intense meetings between over 30 experts in the field with a separate advisory board of other experts in the field.

**Ash Paul** @pash22 · Jul 17, 2023  
2/n .. that you were v satisfied with the outcome of the deliberations of this group because you implied the discussns had been robust in

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- **Adrian H**  
@Adrian\_H  
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2 1 747

**Ash Paul** @pash22 · Jul 17, 2023

2/n .. that you were v satisfied with the outcome of the deliberations of this group because you implied the discussns had been robust in this gup. Twitter is not a gud place 2 debate nuances & I apologise if I mistook what u meant in ur tweet (screenshot given in previous tweet)

1 1 707

**Ryan Townley** @DrTFFromKC · Jul 17, 2023

What I said was factually correct.

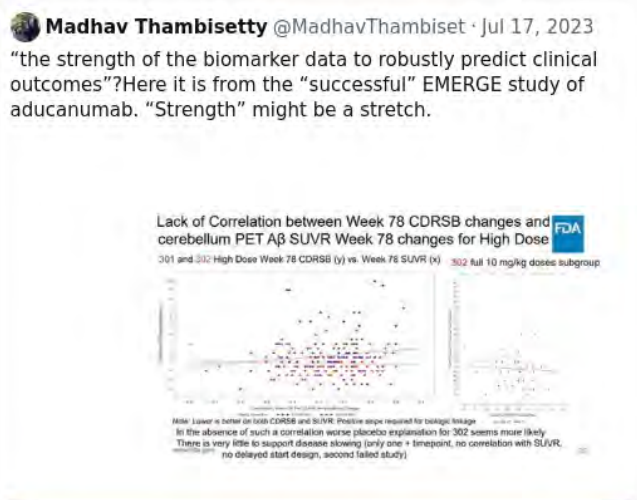
I can also have nuanced opinions that from a brain health view, moving the needle for earlier detection of pathology is very important for our field...

While also having concerns about COI and the risk/benefit of our current treatment options.

2 1 740

**Ash Paul** @pash22 · Jul 17, 2023

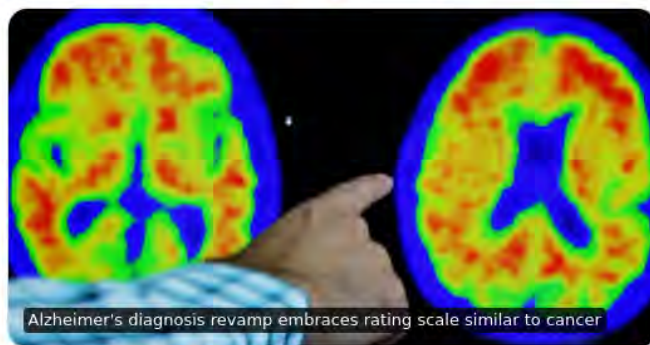
Here's Madhav @MadhavThambiset 's comment on biomarkers a short time back



**Ash Paul** @pash22 · Jul 17, 2023

Alzheimer's diagnosis revamp embraces rating scale similar to cancer

[reuters.com/business/healthcare-pharmaceuticals/alzheimers-diagnosis-revamp-embraces-rating-scale-similar-to-cancer/](https://reuters.com/business/healthcare-pharmaceuticals/alzheimers-diagnosis-revamp-embraces-rating-scale-similar-to-cancer/) via @JDSteenhuysen



From reuters.com

2 1 782

**Ash Paul** @pash22 · Jul 17, 2023

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Alzheimer's diagnosis revamp embraces rating scale similar to cancer

From reuters.com

2 1 782

Ash Paul @pash22 · Jul 17, 2023

@EliLillyandCo expects @US\_FDA decision on Alzheimer's drug Donanemab by end of year as it unveils full PhIII data [endpts.com/eli-lilly-subm...](#) via @leilei\_wuu


endpts.com

Updated: Eli Lilly expects FDA decision on Alzhei Eli Lilly said Monday morning that it has submitted an application for its experimental ...

1 1 1 718

Ash Paul @pash22 · Jul 17, 2023

Experts urge health regulators to approve 'turning point' dementia drugs [theguardian.com/society/2023/j... via @andrewgregory](#)



Experts urge health regulators to approve 'turning point' dementia drugs

From theguardian.com

2 1 814

Ash Paul @pash22 · Jul 17, 2023

Alberto @AlbertoEspay 's tweetorial on Solanezumab and the A4 trial

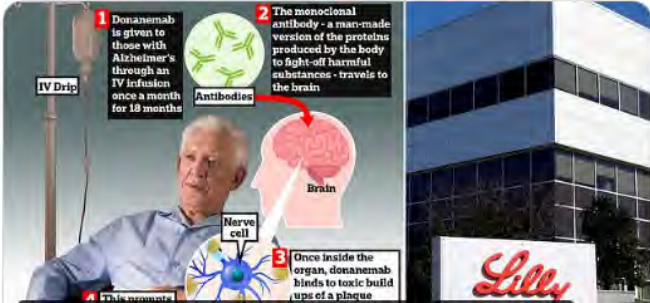
Alberto J Espay @AlbertoEspay · Jul 17, 2023

The hypothesis that amyloid is toxic was tested in the 'A4' trial. The anti-Aβ monomer antibody solanezumab numerically worsened cognition vs. placebo over 4.5 years in people with brain amyloid without symptoms. A summary of the data (1/12). [nejm.org/doi/full/10.10...](#)

1 4 874

Ash Paul @pash22 · Jul 17, 2023

Are we REALLY at a 'turning point in the fight against Alzheimer's'? Breakthrough new drugs halt cruel disease's decline... but experts warn crippling side effects (and cost) may outweigh any benefits [dailymail.co.uk/health/article...](#) via @emilylcraig



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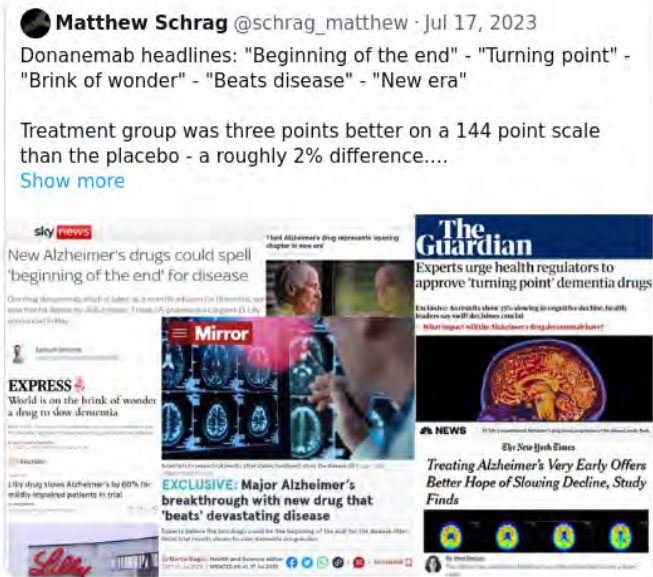
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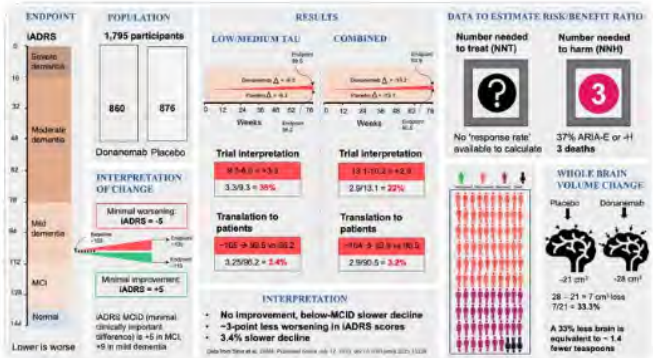
1 1 2 788

Ash Paul @pash22 · Jul 17, 2023  
Here's Matthew @schrag\_matthew 's tweet on the Donanemab trial



2 1 2 1.4K

Ash Paul @pash22 · Jul 17, 2023  
Here's Alberto @AlbertoEspay 's infographic abt the Donanemab trial



Alberto J Espay @AlbertoEspay · Jul 17, 2023  
Donanemab in early symptomatic Alzheimer's disease - Infographic of the phase 3 trial data published by JAMA earlier today.  
Highlights:...

1 1 5 1.4K

Ash Paul @pash22 · Jul 18, 2023  
The hype about the new Alzheimer's drug Donanemab has gone too far: we're still years from a cure [inews.co.uk/news/the-hype-...](https://www.inews.co.uk/news/the-hype-...) via @StuartJRitchie

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**Ash Paul** @pash22 · Jul 18, 2023

The hype about the new Alzheimer's drug Donanemab has gone too far: we're still years from a cure [inews.co.uk/news/the-hype-...](#) via [@StuartJRitchie](#)

The hype about the new Alzheimer's drug has gone too far - we're still y...

From inews.co.uk

2 4 13 2.7K

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**Ash Paul** @pash22 · Jul 18, 2023

If it is clinically effective and cost-effective ie cost/QALY is between £20000 & £30000, then [@NICEComms](#) will order [@NHSEngland](#) to fund it. The million dollar Q is whether it is either!

1 4 895

**Seb Walsh** @seb\_walsh · Jul 18, 2023

Other pertinent Qs for [@NICEComms](#) . Trials too short for meaningful endpoints. Trial populations younger, no co-morbid, no mixed [#dementia](#) Vs realworld at dementia Dx.

Extrapolation beyond trial valid? Trial QALYs applicable to realworld? Costs include Dx/monitoring resources?

1 2 8 2.1K

**Ash Paul** @pash22 · Jul 18, 2023

[@JAMANetwork](#) editorial on Donanemab by Eric [@EWidera](#) et al who I admire greatly but disagree with, in this article [👉](#) "Ushering in a New Era of Alzheimer Disease Therapy"

jamanetwork.com  
Ushering in a New Era of Alzheimer Disease The  
In June 2021, the US Food and Drug  
Administration (FDA) granted accelerated ...

3 1 3 1K

**Lon S. Schneider, MD** @LonSchneiderMD · Jul 18, 2023

Exactly what do you disagree with in [@EWidera](#) commentary?

1 2 904

**Ash Paul** @pash22 · Jul 18, 2023

The conclusion Lon. As Seb as pointed out, his article is very balanced otherwise. Majority of clinicians don't read the full article. They just read the headline and the abstract  
"Science in the Abstract: Don't Judge a Study by its Cover"  
[absolutelymaybe.plos.org/2014/05/12/sci...](#) via [@hildabast](#)

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3

4

1K

**Lon S. Schneider, MD** @LonSchneiderMD · Jul 18, 2023

Got it. What part of the conclusion?

1

1

978

**Eric Widera, MD** @EWidera · Jul 18, 2023

And here I thought the conclusion was the least controversial part of the editorial. Hopefully the issue isn't with the second sentence!

2

7

1K

**Ash Paul** @pash22 · Jul 18, 2023

Ultimately, new treatments such as donanemab will not only change the Alzheimer research landscape but also the clinical one. Accurate and timely diagnosis, thoughtful discussion on individualized risks and benefits, and an emphasis on chronic care management have never been more important.

2

7

1K

**Ash Paul** @pash22 · Jul 18, 2023

It IS the 2nd sentence that's the prob Eric. IMO, you shud have written 'MAY' instead of 'should'. Ur use of the word should reinforces degree of certainly 2 an uncertain prob. Also, choice of title (probably not chosen by u but by the publisher??) is at odds w/ ur super edit'

1

1

812

**Ash Paul** @pash22 · Jul 18, 2023

As a clinical payer, I have these arguments frequently with different clinicians demanding to be funded for this, that & the other, based on choice of innocuous words in the article/editorial

2

1

767

**Eric Widera, MD** @EWidera · Jul 18, 2023

Are you sure you are reading the right editorial? There is no "should" in my conclusion. Also, if anything I would have worded it stronger as a "must" for the need of chronic care management (which is not just giving these drugs)

1

5

870

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individualized risks and benefits, and an emphasis on chronic care management have never been more important.

1 5 829



**Ash Paul** @pash22 · Jul 18, 2023

Many apologies Eric, I mean 'may' instead of 'will'. I used the word 'should' inadvertently

1 1 826



**Eric Widera, MD** @EWidera · Jul 18, 2023

Oh. So it's the first not second sentence. Do you really think though that these drugs aren't going to change the landscape of dementia care (for the good or bad)? For me there is no "may" as it absolutely "will" and that's the part that keeps me up at night

2 6 925



**Scott M. Reid** @Scott\_M\_Reid · Jul 19, 2023

This thread keeps me up at night... looking for the unsubscribe button \*\*

2 3 862



**Ash Paul** @pash22 · Jul 19, 2023

To add to ur insomnia Scott (u can always mute the whole thread so that u can sleep better at night)

"Donanemab for Alzheimer Disease: Who Benefits and Who Is Harmed?" [jamanetwork.com/journals/jama/...](https://jamanetwork.com/journals/jama/...) via @ManlyEpic & @KcD\_PhD

**Donanemab for Alzheimer Disease—Who Benefits and Who Is Harmed?**  
Jama. 2023;329(12):1055-1062. doi:10.1001/jama.2023.1055

**Availability of safe and effective treatments** for Alzheimer disease is an urgent challenge given the global shift toward an older population and increased risk of mild cognitive impairment and dementia as people age.<sup>1-3</sup> Dementia-related burdens are disproportionately felt within historically marginalized communities because structural inequalities related to race, ethnicity, and socioeconomic status increase risk factors for cognitive impairment, increase barriers to diagnosis, and reduce access to care.<sup>4</sup>

It has been encouraging that recent clinical trials of amyloid-clearing monoclonal antibodies have not been able to meet goals of inclusion of racial/ethnic groups. Prospective and well-powered stratified analyses in drug treatment trials are critical for testing differences in drug benefits, assessing frequency and severity of adverse events, and identifying barriers to specialized care that is required to monitor progress. Variability across community and clinical settings and an overreliance on white participants likely responsible for conflicting reports of differences in amyloid levels across racial/ethnic groups<sup>5-8</sup> and, thus, eligibility for this class of drugs.

In this issue of JAMA, Sims et al<sup>9</sup> report phase 3 trial results of donanemab in 1750 participants (91.3% White) with mild cognitive impairment or mild dementia who had evidence of amyloid and tau pathology on positron emission tomography (PET) scans. Seventy-two percent of participants were 18-64 years old. Of those, 96.2% were White and 94.3% were non-Hispanic. The authors report efforts to diversify the trial, but among those randomized to treatment with donanemab, only 23 identified as American Indian or Alaska Native (15-20%), 37 as Asian (8 from the US), 19 as Black (18 from the US), and 15 as Hispanic (15 only). Novel aspects of clinical design included stratification by tau level at baseline (N282 had low/medium tau pathology and 334 had high tau pathology) and ending infusion once amyloid was cleared.

Donanemab was very effective at eliminating its target, cerebral amyloid, but the clinical effect was comparatively weak. By the end of the trial (76 weeks), amyloid plaques were cleared in 80% of the treatment group. Overall, cognition and daily function continued to decline in all participants, but treatment with donanemab delayed progression on the primary outcome (the integrated Alzheimer Disease Rating Scale) by about 6 months. Several important subgroup analyses were prespecified but were not adequately powered. Slowing of decline was more pronounced in those with low/medium tau pathology and less pronounced in APOE ε4 carriers.

groups that showed greater estimates for percent slowing consistent with acceleration of cognitive and functional decline (ie, worsening clinical outcomes) in the donanemab group were those racialized as Black (1-86% [95% CI, -98.1% to 26.2%]) slowing in the low/medium tau group and Hispanic (1-103% [95% CI, -85.2% to 64.7%]) slowing in the low/medium tau group, but the precision of these results is not sufficient to draw conclusions.

Treatment with donanemab was associated with significant safety risks. Thrombotic events were determined to be drug-related among participants who developed serious amyloid-related imaging abnormalities of brain bleeding and swelling. Donanemab decreased whole-brain volume and increased ventricular volume. In the treatment group, amyloid-related imaging abnormalities were seen in about 32% vs 15% in the placebo group and were seen in 43.6% of APOE ε4 homozygotes. Microhemorrhage occurred in 26.3% in the donanemab group vs 12.3% in the placebo group.

Concerns that amyloid-clearing monoclonal antibodies may widen inequalities in Alzheimer disease were recently raised to develop policy recommendations for lecanemab.<sup>10</sup> The study by Sims et al targeted people who had mild symptoms of Alzheimer disease, but missed target groups are typically diagnosed at later disease stages, in part due to the lack of access to care perpetuated by a discriminatory health care system. Structural inequalities led to higher prevalence of amyloid microbleeds,<sup>11</sup> infarcts, and white matter disease<sup>12</sup> among people racialized as Black, narrowing the proportion of this population who meet the study inclusion criteria (about 10% of people screened for this study were excluded, but prespecified details were not reported). PET scans are required to determine the presence of cerebral amyloid, and frequent monitoring via magnetic resonance imaging (MRI) is needed to monitor occurrence and severity of amyloid-related imaging abnormalities, making access and proximity to neuroimaging centers paramount. Typical placement of neuroimaging centers is predominantly white, upper-class neighborhoods may disenfranchise people whose communities are less likely to be served by medical centers with timely access to Alzheimer disease specialists, PET, and MRI.<sup>13,14</sup>

Similar to previous trials of lecanemab and aducanumab, this donanemab trial does not provide sufficient evidence of safety or efficacy among people racialized as American Indian or Alaska Native, Asian, Black, or Hispanic. Given the wide availability of these drugs following US Food and Drug Administration approval and the disproportionate burden of cognitive impairment and dementia due to Alzheimer disease in many of these groups,<sup>15</sup> it is critical that clinical

2 8 1.8K



**Alberto J Espay** @AlbertoEspay · Jul 19, 2023

Great editorial. Plaque clearance in 80% but puny slowness of decline (or none in American Indian or Alaska Native, Asian, Black, and Hispanic). Is it known if the "better" "low/medium tau" group" is also younger or has a shorter symptom duration? Can't find this in the paper.

1 7 1.3K



**Ash Paul** @pash22 · Jul 19, 2023

Alzheimer's drug trials target older Californians: Do they understand

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the paper.

1 1 7 1.3K

Ash Paul @pash22 · Jul 19, 2023

Alzheimer's drug trials target older Californians: Do they understand what they're signing up for? [latimes.com/business/story...](https://www.latimes.com/business/story...) via @MelodyPetersen



Alzheimer's drug trials target older Californians. Do they understand wh...

From latimes.com

1 2 10 6.7K

Madhav Thambisetty @MadhavThambiset · Jul 20, 2023

Below on risks of enrolling in the AHEAD study testing Lecanemab in cognitively normal individuals considered to be at risk of AD based on brain amyloid levels. From pages 14 & 15 of 20-page "study guide" [tinyurl.com/yc52evu4](https://tinyurl.com/yc52evu4)

Risks of Participation

The informed consent form details the AHEAD Study's risks. Here, we focus on four:

1. Participant study information is not released to personal physicians without the participant's permission, and we code participant study information to protect confidentiality. However, it is possible information about a participant could be entered into an individual's medical record, particularly if the individual experiences

2. Although we will do everything possible to protect your confidentiality, information about amyloid status or participation in this study could potentially influence the ability to obtain life insurance, health insurance, or long-term care insurance. If you are think about purchasing any of these policies, you might do it before enrolling.

3. Information about amyloid status could also affect your employability.

4. All drugs have risks. For investigational drugs, one of the goals of the study is to

2 3 8 1.6K

Lon S. Schneider, MD @LonSchneiderMD · Jul 20, 2023

These are the risks in the US of enrolling in any Alzheimer's trial.

2 3 937

Madhav Thambisetty @MadhavThambiset · Jul 20, 2023

Except this is a population without Alzheimer's disease. Cognitively normal folks enrolled for 4 years to receive an mab or placebo based on amyloid status with an explicit risk of losing employment or employability.

4 1 8 1.1K

David Rind @dmrind · Jul 20, 2023

Unlikely breaches of confidentiality are not a central issue for consent.

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Document title: (2) Adrian H on X: &quot;@DanClintonRN @pash22 @ProfRobHoward @LogarithmicDis @LonSchneiderMD @MadhavThambiset @RenegadeSynaps... Capture URL: https://twitter.com/Adrian\_H/status/1712881971347517840 Capture timestamp (UTC): Mon, 29 Apr 2024 15:12:04 GMT Page 88 of 125



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4

1

8

1.1K

David Rind

@dmrind · Jul 20, 2023

Unlikely breaches of confidentiality are not a central issue for consent.  
This is an RCT trying to answer a question pretty much everyone is asking: can lec (or don) prevent AD if started early? The answer may be "no"; they may even cause harm. We need RCTs and there are risks.

2

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6

828

Madhav Thambisetty

@MadhavThambiset · Jul 20, 2023

I mentioned AHEAD in the context of the tweet re: informed consent & whether AD patients know what they are signing up for in RCTs. I'd find it ethically challenging to consent a cognitively normal person to enroll in an RCT for 4 years & tell them it could risk their employment

2

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787

Dan Clinton - The Awesome Nursing

@DanClintonRN · Jul 20, 2023

AND DEATH! They're risking death and irreversible brain damage. Asymptomatic people. And this study wants to label them as having a progressive terminal illness based on imaging & give them a drug kills 1 in 592 and has a > 1% chance of severely irreversibly damaging their brain.

1

1

2

749

David Rind

@dmrind · Jul 20, 2023

If you don't feel there's equipoise, you should recommend that people not participate in the trial. Personally, I would make sure people are clear about the risks, but I would not strongly advise for or against participation.

1

1

3

748

Alberto J Espay

@AlbertoEspay · Jul 20, 2023

Four anti-amyloid trials targeting normal people with amyloid, including the A4 study in preclinical AD and the API ADAD on a preclinical Colombian PSEN1 E280A cohort, have given a clear answer: removing amyloid is futile at best, and often detrimental.

2

1

6

1.9K

Alberto J Espay

@AlbertoEspay · Jul 17, 2023

The hypothesis that amyloid is toxic was tested in the 'A4' trial. The anti-A $\beta$  monomer antibody solanezumab numerically worsened cognition vs. placebo over 4.5 years in people with brain amyloid without symptoms. A summary of the data (1/12). [nejm.org/doi/full/10.1093/brain/awz010](https://doi.org/10.1093/brain/awz010)

2

1

6

1.9K

Nicolas Villain

@nvillain\_alz · Jul 20, 2023

The A4 study did not 'remove' any amyloid plaque but did slow down B-amyloid aggregation over time. This wasn't associated with any clinical effect (nor ARIA). Leca and dona do have the property to 'remove' aggregated B-amyloid. Same for other studies with low-dose gante and sola

2

1

8

881

Alberto J Espay

@AlbertoEspay · Jul 20, 2023

Pardon my poor choice of words. Solanezumab lowered amyloid levels not by 'removal' but by being prevented from forming. The point is that lowering amyloid or the A $\beta$  monomer (what this antibody binds to) is still an anti-protein approach and proteins (at any stage) are not toxic.

2

1

8

881

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@810964733763B

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@Adrian\_H

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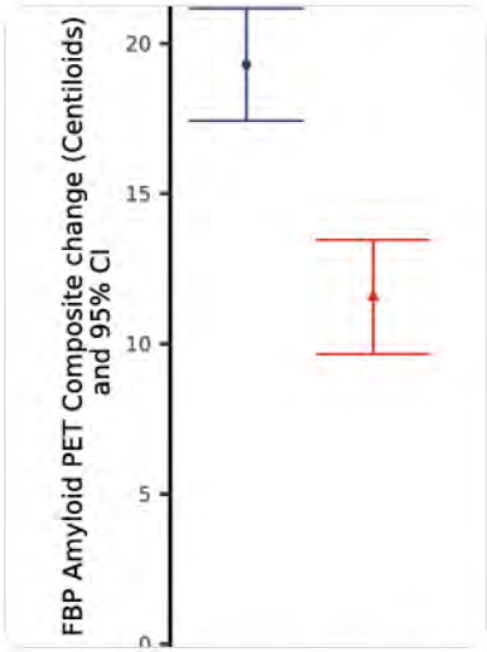
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antibody binds to) is still an anti-protein approach and proteins (at any stage) are not toxic.



1 1 986



**Nicolas Villain** @nvillain\_alz · Jul 20, 2023

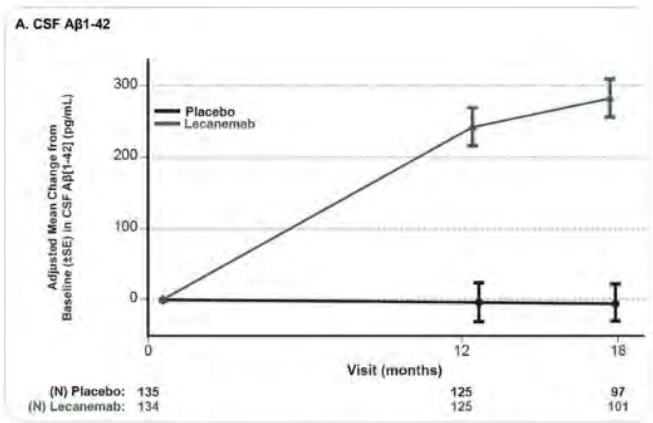
That's your hypothesis, not a fact:) Fact is: aggregated forms of ABeta are cleared from the brain by dona/leca/adu, not by sola/crene. This may or not be biologically relevant, but in symptomatic patients we see a small but consistent effect for dona/leca/adu, not for the others

2 8 1K



**Alberto J Espay** @AlbertoEspay · Jul 20, 2023

There are two sides to any story. Aggregated forms of Abeta come from normal Abeta --invariably low in AD. A positive effect of lecanemab was that it increased Abeta. But this observation is against the only side of the story we care about, hence it's buried in Figure S5.



3 5 1.1K



**Joseph Therriault** @JosephTherr · Jul 21, 2023

Alberto, hasn't the low CSF AB42 idea been falsified? According to prevalence estimates (see Janssen jama neuro 2022) low CSF AB42 is even more compatible with normal cognition than abnormal amyloid-PET.

1 4 930

Relevant people



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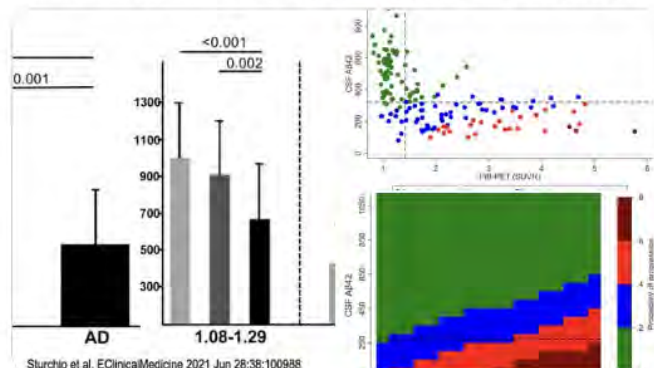


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**Alberto J Espay** @AlbertoEspay · Jul 21, 2023

I didn't come away with that conclusion from that paper. In both the ADNI and DIAN datasets, high A $\beta$ 42 correlates with normal cognition at any level of amyloid PET. In the DIAN cohort, the higher the A $\beta$ 42 levels, the more likely it is that normal cognition will be preserved.



**Joseph Therriault** @JosephTherr · Jul 21, 2023

I've seen you cite this multiple times, and i agree that it's an odd effect, but do you ever wonder that you're over-interpreting it? Do you see it with the 42/40 ratio?



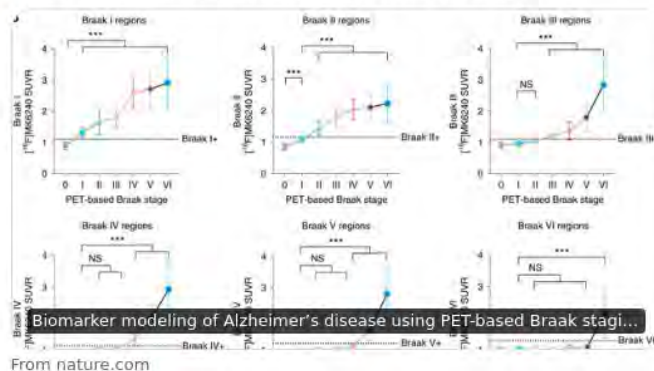
**Joseph Therriault** @JosephTherr · Jul 21, 2023

Look at figure 1 of the 2022 janssen jama neuro paper I don't see how you can explain higher prevalence of low A $\beta$ 42 in cog unimpaired that amyloid-PET positivity. The model is low CSF A $\beta$ 42 comes first



**Joseph Therriault** @JosephTherr · Jul 21, 2023

Data from our centre supports this too (see figure 5)



**Alberto J Espay** @AlbertoEspay · Jul 21, 2023

Did your analysis use absolute numbers or only the CSF A $\beta$ 42/A $\beta$ 40 ratio? Do you have the data on individual CSF values?



**Joseph Therriault** @JosephTherr · Jul 21, 2023

Yes. Same results with both

## Relevant people



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@Adrian\_H

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1 3 666

Joseph Therriault @JosephTherr · Jul 21, 2023

Yes. Same results with both

1 1 686

Alberto J Espay @AlbertoEspay · Jul 21, 2023

Can you point me to the paper location of the results with the individual values? Can't find it.

1 1 706

Joseph Therriault @JosephTherr · Jul 21, 2023

I think we only published the ratio results, but check the supplement for individual values. You will see a very early plateau of CSF amyloid

1 1 749

Joseph Therriault @JosephTherr · Jul 21, 2023

If you're curious, i can run an analysis and show you results without the ratio. But most importantly, check fig 1 of janssen 2022 jama neuro!

2 928

Alberto J Espay @AlbertoEspay · Jul 21, 2023

I'd like to know your analysis of individual values. Meanwhile, can you walk me through the part of Figure 1 that should tell me low CSF Ab42 is more compatible with normal cognition than abnormal amyloid-PET?

[jamanetwork.com/journals/jaman...](https://jamanetwork.com/journals/jaman...)

3 775

Joseph Therriault @JosephTherr · Jul 21, 2023

To make sure we're on the same page, what do you mean by individual values?

And in this figure, you can see the prevalence of low CSF AB42 is higher in asymptomatic individuals than amyloid PET

1 1 723

Alberto J Espay @AlbertoEspay · Jul 21, 2023

It is hard to interpret a figure using "adjusted CSF cutoffs." The text says, "CSF-based amyloid abnormality estimates were, on average, 10% higher than PET-based estimates in persons with normal cognition." But how does this translate into low CSF Ab42 values = normal cognition?

1 2 742

Alberto J Espay @AlbertoEspay · Jul 21, 2023

And by individual values, I mean the absolute concentration of Ab42, measured in pg/ml.

1 2 777

Joseph Therriault @JosephTherr · Jul 21, 2023

Ok sounds good about pg/ml 🙄

I'm not suggesting low CSF AB42 = normal cognition. The data suggests that low AB42 is more common in people with normal cognition than amyloid-PET abnormality is.

1 2 844

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I'm not suggesting low CSF Aβ42 = normal cognition. The data suggests that low Aβ42 is more common in people with normal cognition than amyloid-PET abnormality is.

1 2 844

Joseph Therriault

@JosephTherr

· Jul 21, 2023

...

This fits with the idea that low CSF Aβ42 comes before amyloid-pet abnormality (it is an even earlier marker)

1 2 868

Alberto J Espay

@AlbertoEspay

· Jul 21, 2023

...

I understand now. Yes, as Aβ42 transforms into amyloid, its levels in CSF go down, and its measurable fraction by PET increases. Low Aβ42 can happen in normal people but once below a certain threshold (~800 pg/ml) symptoms appear. No one with AD has high Aβ42 levels.

2 2 999

Joseph Therriault

@JosephTherr

· Jul 22, 2023

...

I agree with you about the first half! Aβ42 aggregates into plaques (more seen with PET) and lower concentrations are in CSF. But data from our centre does not support 800 pg/ml as causing symptoms (nearly 1/3 of cog normals have CSF Aβ42 below 800 pg/ml)!

1 3 939

Nicolas Villain

@nvillain\_alz

· Jul 22, 2023

...

Absolutely, and I can confirm that from everyday clinical practice using CSF: I've seen so many individuals with isolated low Aβ42 (in our center the thr is 650) who were cog normal or had another disease (see my answer to Karriem), and, conversely, AD symptomatic with high Aβ42

3 1 1K

Alberto J Espay

@AlbertoEspay

· Jul 22, 2023

...

Agreed. No biomarker is perfect at defining a threshold for disease. Could we also agree that there is more at stake from low soluble Aβ42 (the functional protein) than from high insoluble amyloid (nonfunctional)? High amyloid is compatible with normal cognition; low Aβ42 is not.

1 1 842

Nicolas Villain

@nvillain\_alz

· Jul 22, 2023

...

Hum, the Jansen reference mentioned by @JosephTherr clearly shows that low Aβ42 is even more compatible with normal cognition than high amyloid PET? Besides, my clinical experience also goes in this direction (I've seen many individuals with low Aβ42 and normal cog testing)

2 1 2 1.2K

Alberto J Espay

@AlbertoEspay

· Jul 22, 2023

...

Resort a discussion to "my personal experience" (especially if someone's personal experience is 'better' than the other) demotes data and promotes anecdotes. We all see outliers. Experience. We also can separate the forest from the trees. Data.

4 1 3 1.4K

Nicolas Villain

@nvillain\_alz

· Jul 22, 2023

...

@AlbertoEspay, with all due respect, I also previously brought up the Jansen reference in our discussion. This particular study surveyed 20,000 individuals across various cohorts, making its data particularly robust and reliable.

1 4 700

Timothy Daly, PhD

@PhilAlz

· Jul 22, 2023

...

I think this fascinating debate shows that @AlbertoEspay's point

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@Adrian\_H

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particularly robust and reliable.

1 4 700

**Timothy Daly, PhD** @PhilAlz · Jul 22, 2023  
I think this fascinating debate shows that @AlbertoEspay's point about testing hypotheses is valid. His claim that low "AB42 --> AD" has some data in favor of it, and the data you and @JosephTherr presented against it. The RCT was designed to solve this. Is it not worth testing?

4 775

**Timothy Daly, PhD** @PhilAlz · Jul 22, 2023  
(I guess my question to @nvillain\_alz & @JosephTherr is: if such replacement therapies became available, would you see merit in testing AB42 replacement therapy in ARAD/AD patients?)

1 746

**Simon Mead** @smead2 · Jul 22, 2023  
The idea is so implausible to me I cannot see going straight to human can be justified. Priority now for those that see any merit in this would be to establish animal and cellular models that lend some support and evidence of safety. I haven't seen anything yet.

1 843

**Alberto J Espay** @AlbertoEspay · Jul 22, 2023  
Here is a test of this hypothesis in mice. "Exogenous Aβ142 monomers improved the impaired memory not only in cDKO mice without Aβ142 deposition but also in the APP/PS1/Tau triple transgenic 3 × Tg-AD mice with Aβ142 deposition, mediated by α7-nAChR."  
[sciedirect.com/science/article/...](https://sciedirect.com/science/article/...)

1 868

**Simon Mead** @smead2 · Jul 22, 2023  
Sure, this paper is something not nothing

2 809

**Andrew Stern, MD PhD** @andrewmstern · Jul 23, 2023  
I've been sucked in again, but: brain Ab42 is HIGHER in AD than control. The opposite of CSF.

1 743

**Simon Mead** @smead2 · Jul 23, 2023  
Interesting, I didn't know that Andrew, do you have a citation I'd like to read more about that

1 772

**Andrew Stern, MD PhD** @andrewmstern · Jul 23, 2023  
Been known for a long time. Eg  
[pubmed.ncbi.nlm.nih.gov/10589538/](https://pubmed.ncbi.nlm.nih.gov/10589538/)  
  
See also familial mutations that increase Ab42 production, and Down syndrome.

...

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1 1 5 1.3K

**Simon Mead** @smead2 · Jul 23, 2023

Thanks I have always assumed, perhaps wrongly that low CSF abeta in AD was a because monomer is drawn into aggregates in the brain parenchyma

3 1 858

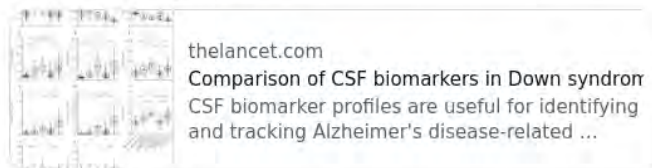
**Alberto J Espay** @AlbertoEspay · Jul 24, 2023

I wonder if we should engineer humans without amyloid beta. It seems evolutionary forces preserving this 42-amino acid peptide since prehistoric genomes got it all wrong!

1 2 813

**Alberto J Espay** @AlbertoEspay · Jul 24, 2023

Also, I should have my dyslexia looked into. I thought that besides PSEN1, the levels of AB42 in APP duplication and Down syndrome decrease over time. Can you help me find in this paper where it shows the levels go up instead?



2 2 914

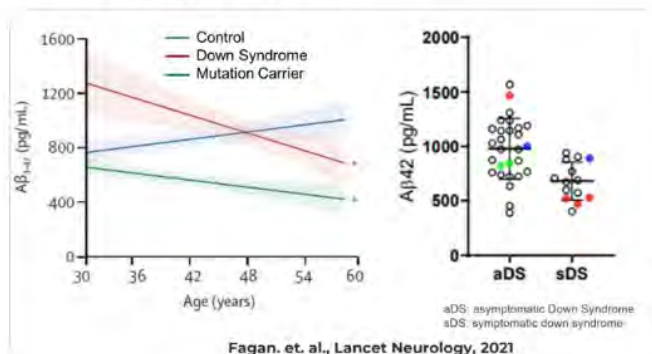
**Simon Mead** @smead2 · Jul 24, 2023

As for Down's - the gene is duplicated - the expression of APP will be increased from birth. High levels trigger the disease pathology. CSF levels of abeta then go down as part (a consequence of) the disease process once abeta aggregation is established.

1 1 742

**Kariem Ezzat** @Kariem\_Ezzat · Jul 24, 2023

Down's patients are asymptomatic (in terms of dementia) all the while they have high levels of CSF Aβ42 & become symptomatic only when these levels start to drop.



1 3 747

**Kariem Ezzat** @Kariem\_Ezzat · Jul 24, 2023

If Aβ was so toxic, like any other toxin the worst stage of the disease should correspond to its highest levels not its lowest levels.

1 3 8 1.7K

**Jan** @810964733763B

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- Kariem Ezzat** @Kariem\_Ezzat · Jul 24, 2023  
If A $\beta$  was so toxic, like any other toxin the worst stage of the disease should correspond to its highest levels not its lowest levels.
- Simon Mead** @smead2 · Jul 24, 2023  
I don't think anyone proposes abeta monomer is toxic, at least not anyone I know. why would you think that?
- Kariem Ezzat** @Kariem\_Ezzat · Jul 24, 2023  
Toxicity has always been viewed as a function of A $\beta$  concentration, which led to the development of A $\beta$  monomer lowering/sequestering agents such as  $\beta$  &  $\gamma$  secretase inhibitors & solanezumab, many of which actively worsened cognition in clinical trials.
- Simon Mead** @smead2 · Jul 24, 2023  
Not really, people tried to lower abeta to reduce the propensity for it aggregating into multimeric assemblies - some of which not necessarily all - are toxic. I don't think anyone ever viewed the monomer as toxic in this form.
- Alberto J Espay** @AlbertoEspay · Jul 24, 2023  
You are correct, Simon. The goal was to reduce amyloid (accomplished) via reducing A $\beta$ 42 monomers (also accomplished). Results: patients worsened, and brain atrophy accelerated. Amyloid reduction, A $\beta$ 42 reduction, or reducing both is detrimental. [nejm.org/doi/full/10.10...](https://doi.org/10.1093/ajph.2023.133.1471)
- 
- Simon Mead** @smead2 · Jul 24, 2023  
We don't know why patients did worse in this drug trial you cannot be certain this was abeta monomer. Enzyme has several functions and off target effects.
- Kariem Ezzat** @Kariem\_Ezzat · Jul 24, 2023  
But again, toxicity (whatever the mechanism), & hence disease severity, should be proportional to the concentration of the causative substrate. More monomer, more aggregates, more tox., more disease. However, the disease course is the exact opposite, more monomer --> less disease.
- Simon Mead** @smead2 · Jul 24, 2023  
That's far too simplistic view imo. We don't of course directly measure toxicity we see cognitive decline which is the result of maybe a decade or more or accrued damage to neuronal networks. Never mind the relationship between monomer and aggregated

## Relevant people

- Adrian H** @Adrian\_H  
Je ne te parle pas, je chante pour moi-même, je chante pour moi-même! Et je pense! il n'est pas défendu de penser! I don't like bullies. I block anon idiots.
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Ash Paul @pash22 · Jul 26, 2023

Only a few in France Nicolas?? It is estimated that 4-5% of patients will be suffering with health anxiety (formerly called hypochondriac) and they are clogging up GP practices in UK

1 779

Nicolas Villain @nvillain\_alz · Jul 26, 2023

"Worried-well" does not refer to anxiety disorders (since they do a complaint and symptoms): this term relates to asymptomatic patients going to the memory clinic to prevent dementia because of their family history or just because of a general interest in their health

1 775

Ash Paul @pash22 · Jul 26, 2023

Oh OK. In UK, we define it somewhat differently. Patients with this label could range from someone with a concerning symptom that turns out to be nothing, to someone with severe health anxiety. The term suggests that these patients are well

1 889

Nicolas Villain @nvillain\_alz · Jul 26, 2023

Yes, the worried-well term suggests that they do not fulfill the criteria for any neurological and/or psychiatric disease/disorder

1 863

Seb Walsh @seb\_walsh · Jul 26, 2023

Feel this is all missing the point

Drs want to give these 'preventive' drugs (if long term benefits shown) early enough in disease

Vast majority of pts present after this time (& have mixed disease)

Pharma want max markets

To me, this says D) is where this agenda is heading

2 1 2 1.2K

Matthew Herper @matthewherper · Jul 26, 2023

I don't think the companies have been quiet about their long-term goal. They are aiming for subcutaneous drugs, with screening done with blood tests. They also want to show efficacy earlier in disease. They'll need data to back that up -- won't happen based on these trials.

1 2 3 1.2K

Simon Mead @smead2 · Jul 26, 2023

Exactly agree, and this future may be great - emphasis on may - if we can do this conveniently, safely, cost effectively and of course if it works. But plenty to be getting on with whilst we wait for these data.

1 2 931

Seb Walsh @seb\_walsh · Jul 26, 2023

But the key word in Matthew's tweet is "screening"

Still left with fact that screening people at start of cascade = most people picked up will die without dementia. How can this ever be net beneficial? Unless drugs are super cheap, with almost no bad side effects (e.g. statins)

1 2 3 1.2K

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@Adrian\_H

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Still left with fact that screening people at start of cascade = most people picked up will die without dementia. How can this ever be net beneficial? Unless drugs are super cheap, with almost no bad side effects (e.g. statins)

1

2

3

1.3K

Simon Mead

@smead2 · Jul 26, 2023

...

The idea I think is that we screen with improved biomarkers that will better predict who will convert over x years. At the moment we can't screen asymptomatic people well enough to justify the risky, expensive and cumbersome treatments and we lack any evidence. More research...

1

1

763

Seb Walsh

@seb\_walsh · Jul 26, 2023

...

Ok, so we add 'better predictive biomarkers' to list of needed thihngs to make this class of drugs clinically useful

1

Better predictive biomarkers

Bigger effect size

Demonstrate long-term effects

Less side effects/toxic

Not IV

Cheaper

...

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2

1

7

1.1K

Nicolas Villain

@nvillain\_alz · Jul 26, 2023

...

2/2  
5) not IV: active vaccines or self administered SC  
6) cheaper: active vaccines  
🤖👤

2

2

920

Ryan Townley

@DrTFromKC · Jul 26, 2023

...

100% agree with this view and possible scenario.

But it's much easier being pessimistic...

Especially when you are not regularly diagnosing and treating patients with the disease.

1

2

764

Ash Paul

@pash22 · Jul 26, 2023

...

I know. Especially when the empirical evidence abt 'optimism bias' points the other way! I think I was discussing the evid on another twitter thread w/ Simon and Rob.

2

2

884

Matthew Herper

@matthewherper · Jul 26, 2023

...

Another assumption I want to challenge: I think financial analysts tend to see the population in the trials, as a huge and lucrative group. Not sure we need to move further upstream from a financial perspective.

But better screening + subQ will be needed.

Am I wrong?

2

1

958

Robert Howard

@ProfRobHoward · Jul 26, 2023

...

Until the treatments get a whole lot better, nobody is going to make huge amounts of money from Alzheimer's disease.

3

8

1.2K

Relevant people

Adrian H

@Adrian\_H

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Document title: (2) Adrian H on X: &quot;@DanClintonRN @pash22 @ProfRobHoward @LogarithmicDis @LonSchneiderMD @MadhavThambiset @RenegadeSynaps...  
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- Robert Howard** @ProfRobHoward · Jul 26, 2023  
Until the treatments get a whole lot better, nobody is going to make huge amounts of money from Alzheimer's disease.
- Madhav Thambisetty** @MadhavThambiset · Jul 27, 2023  
If genetic validation is a gold standard that guides Rx target validation, it's also a mystery how amyloid-targeting mabs appear to have the least efficacy & induce the greatest harm, dose dependently in APOE4 carriers. APOE4 is after all the strongest AD genetic risk factor 🤔
- CLARITY AD ARIA BY APOE BY CDR...** Done
- Simon Mead** @smead2 · Jul 27, 2023  
There is a very important piece of understanding here I agree - amyloid load, inflammatory responses, vessel damage, more advanced tau pathology- lots of ideas how this might work
- Madhav Thambisetty** @MadhavThambiset · Jul 27, 2023  
Seems an inherent paradox though doesn't it? The strongest known genetic risk factor for late onset AD also predicts greatest harm and least efficacy in those at highest risk and earlier age of brain amyloid accumulation.
- Simon Mead** @smead2 · Jul 27, 2023  
I don't see the paradox here, yet, a puzzle to be solve maybe. The apoe4 risk for AD is frustratingly difficult to pin down we have too many hypotheses about mechanisms with support.
- Ash Paul** @pash22 · Jul 27, 2023  
Not sure abt ur objection to the word paradox Simon. The defo of paradox according to @OED is a statement or situation that may be true but seems impossible or difficult to understand because it contains two opposite facts or characteristics. Does it not hold in this case?
- Kariem Ezzat** @Kariem\_Ezzat · Jul 27, 2023  
I'm not sure the appeal to complexity can save this theory from its paradoxes, neither will mere hope that drugs based on it will one day work spectacularly. It's not a complex theory, it's based on one assumption: amyloid Must be toxic, any other explanation is excluded. 1/3
- Kariem Ezzat** @Kariem\_Ezzat · Jul 27, 2023  
Complexity is injected at a later stage to protect this simple notion from being assailed by data that contradicts it. For ex. ApoE2 is a protective variant associated with sol. Aβ. Isn't more sol. Aβ supposed to lead to more sol. oligomers -> more tox -> more

## Relevant people

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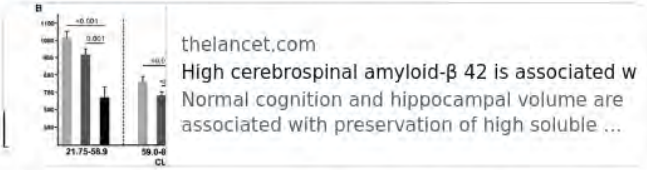
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- Kariem Ezzat** @Kariem\_Ezzat · Jul 27, 2023  
Complexity is injected at a later stage to protect this simple notion from being assailed by data that contradicts it. For ex. ApoE2 is a protective variant associated with  $\beta$  sol. A $\beta$ . Isn't more sol. A $\beta$  supposed to lead to more sol. oligomers -> more tox -> more disease? 2/3
- Kariem Ezzat** @Kariem\_Ezzat · Jul 27, 2023  
There're many other paradoxes that we published about & briefly discussed here: [kezzattheblog.blogspot.com/2022/09/heresy...](https://kezzattheblog.blogspot.com/2022/09/heresy...) & there're alternative concepts (loss-of-function for ex.) that are also simple but can accommodate the complexity of the data much better & with far less contradictions. 3/3
- Alberto J Espay** @AlbertoEspay · Jul 27, 2023  
This blog is so clear. As a clinician, the most remarkable "paradox" to the amyloid hypothesis is that most of us with brain amyloid will never develop Alzheimer's. A solution to that paradox is in [@andrea\\_sturchio](#)'s analysis of the ADNI cohort.
-   
thelancet.com  
High cerebrospinal amyloid- $\beta$  42 is associated w  
Normal cognition and hippocampal volume are associated with preservation of high soluble ...
- Lon S. Schneider, MD** @LonSchneiderMD · Jul 27, 2023  
Maybe we should strike the word "paradox" from these threads? Its uses here are mostly as rhetorical devices that don't really stand up to reason. Seems mostly this is talk about confounds and biases in observational research and making unwarranted comparisons.
- Dan Clinton - The Awesome Nursing** @DanClintc · Jul 27, 2023  
Doesn't believing in the amyloid cascade hypothesis now require ignoring both that many with amyloid don't develop dementia and that those who achieved "amyloid clearance" continued to decline neurologically? Logically, that makes amyloid neither necessary nor sufficient.
- Nicolas Villain** @nvillain\_alz · Jul 27, 2023  
Respectfully, that's what ancient Greeks named sophism. Though not a big fan of the ACH, amyloid is, of course, central to Alzheimer's: necessary for sure but not sufficient indeed.
- Dan Clinton - The Awesome Nursing** @DanClintc · Jul 27, 2023  
I'm not seeking to be deliberately deceive. I'm pointing out that this new data shows Alzheimer's disease continues to progress in the absence of amyloid, 27% of cognitively intact 75-year-olds have amyloid, and > 90% remain without any sort of cognitive impairment 5 years later
- Nicolas Villain** @nvillain\_alz · Jul 27, 2023  
Well, you may not do it intentionally; in that case, we'll call it paralogism. Point taken.  
Still, have you ever seen dementia with Braak stage 6 of tauopathy without amyloid (out of anti-amyloid therapies context)?

## Relevant people

- Adrian H** @Adrian\_H  
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Well, you may not do it intentionally; in that case, we'll call it paralogism. Point taken.  
Still, have you ever seen dementia with Braak stage 6 of tauopathy without amyloid (out of anti-amyloid therapies context)?

1 1 2 1.3K

**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 27, 2023 ...  
You're at a depth beyond my understanding at "Braak stage 6 of tauopathy." But that doesn't resolve the somewhat circular nature of the definition, or that this new research shows that degeneration at least persists in the absence of amyloid

3 1 755

**David Jones** @DavidJonesBrain · Jul 28, 2023 ...  
@DanClintonRN you may find this lecture helpful:

youtube.com  
Should amyloid be targeted in Alzheimer's disease  
This is a recording I did for an invited talk at the 48th annual meeting of Clinical Neurological ...

2 3 9 1K

**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 28, 2023 ...  
@DavidJonesBrain I enjoyed your talk! Lots of intelligent thoughts. Now that amyloid clearance has been shown not to halt or reverse symptomatic Alzheimer's doesn't that argue against it being a therapeutic target? 1/n

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**YouTube**

**Some Active Broader Questions in the Field**

- Is amyloid targeting a viable strategy to prevent, halt, and/or reverse cognitive decline in symptomatic AD?
- Does timing of therapy (pre- vs. early- vs. late-symptomatic) have an influence on clinical response?
- Is amyloid targeting sufficient in AD treatment?
- Other mechanisms: tau, aging/senescence, inflammation, connectivity, soluble entities, etc.
- Combination therapies (as in other complex diseases like hypertension or HIV/AIDS) → precision medicine

VTAMAR (tapinarof) cream, 1%

1 377

**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 28, 2023 ...  
Can you see how changing from a nonspecific, catchall clinic definition that kind of just meant dementia NOS to a biologic definition makes sense, but it then somewhat artificially links amyloid to Alzheimer's? Now dementia + amyloid = Alzheimers 2/n

Done AA youtube.com

**YouTube**

**Conceptualizing AD as a dynamic Biological Process**

- Historical context:** AD as a clinicopathologic entity
  - Amnestic dementia → hallmark features of autopsy
  - Aβ plaques + tau NFTs, basal forebrain neurons (Aβ)
- Current concept:** AD as a specific biological disorder/process
  - Defined by presence of amyloid and "AD" tau pathology
  - This does NOT require CAUSATION
  - Presymptomatic → mild symptoms → dementia
  - Does not always present as an amnestic dementia
  - Can detect with high confidence in life (biomarkers)
  - Imaging and/or fluid biomarkers

1 376

**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 28, 2023 ...  
Shouldn't the accelerated approval be rescinded now that it's been shown amyloid clearance was inversely associated with neurologic status? Those w/ amyloid clearance still declined 3/n

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@Adrian\_H **Follow**  
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**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 28, 2023 ...  
Shouldn't the accelerated approval be rescinded now that it's been shown amyloid clearance was inversely associated with neurologic status? Those w/ amyloid clearance still declined 3/n

Important Details About the FDA Approval

- For mild symptomatic stages of AD (MCI or mild dementia due to AD)
- Drug label has not included specific comment on biomarker status
- Broadly agreed in the field that establishing amyloid positivity is critical
- Approval was via accelerated pathway based on reduction of brain amyloid plaques
- Effect on a surrogate endpoint [...] reasonably likely to predict a clinical benefit
- FDA: "There remains some uncertainty about the drug's clinical benefit"
- FDA expectation was that treatment may yield clinical benefit beyond 18 months
- Approval indicated need for more data on clinical efficacy
- There are nontrivial potential side effects associated with treatment
- FDA approval of aducanumab does not exist in a vacuum

YTAMAR (tabinor) cream, 1%

**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 28, 2023 ...  
Given the progression of dementia after amyloid clearance does that argue against mechanisms which seem amyloid necessary for neurodegeneration? Remember, it's necessary for Alzheimer's by definition 4/5

Should amyloid be targeted in Alzheimer's disease?

- AD biomarkers can be thought of as markers of the Alzheimer's pathway to dementia (even before dementia has occurred)
- If amyloid is NOT associated with the AD pathway, then amyloid therapeutics need not be considered. Holding this view is difficult given current evidence.
- If an amyloid marker IS associated with the AD pathway, then measuring it has a role in clinical decision making independent of causality.
- However, the association NEEDS to be of a causal nature to make amyloid a therapeutic target.

**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 28, 2023 ...  
Lastly, how do you interpret Donanemab's effects? Now that amyloid clearance failed to reverse, halt, or even meaningfully slow cognition which model or models do you think remain plausible? 5/5

**David Jones** @DavidJonesBrain · Jul 28, 2023 ...  
It's all discussed in the talk. I am glad you enjoyed it. If you have additional more in depth question you should check out the primary literature cited. Here is a primer we recently did that might be a place to start:

Alzheimer disease

Prevalence (%)

Autopsy-confirmed AD  
Other; FTLD, pure DLB, etc.

From nature.com

**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 28, 2023 ...  
Have your views not changed now that donanemab caused amyloid clearance in 76% yet the donanemab group continued to experience cognitive decline at a rate of 70/173 months and some that 46% of

Relevant people

**Adrian H** @Adrian\_H 

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**Dan Clinton - The Awesome Nursing** @DanClintonRN · Jul 29, 2023 ...

You can lead a neurologist to water, but you can't make him see his circular logic. Enjoy another 50 years of total failure. You've removed amyloid and the dementia kept progressing. Most with amyloid will never develop dementia. You all have created a tautological definition 1/2

3

5

1.2K




**Timothy Daly, PhD** @PhilAlz · Jul 29, 2023 ...

Dan, Nicolas is not "the problem" with AD research. He promotes a balanced definition of AD, grounded in clinical & biological reality for patients & is a vocal critic of reductionist approaches. As a patient-facing clinician, I don't think he will "enjoy" the lack of treatments.

1

1

579




**Timothy Daly, PhD** @PhilAlz · Jul 29, 2023 ...

Dan, you should send a paper to a journal with your ideas and contribute to scholarly debate. Easy to smell a bad egg, hard to lay a fresh one.

2

564




**Simon Mead** @smead2 · Jul 29, 2023 ...

This isn't unusual is it at this phase of innovation you will refer to HIV AIDS of course, I might cite beta-interferon and MS. Our main disagreement I think is on where this is going beyond the facts we know. It's a 30 yr disease we have a snapshot of possible changes in course

1

501




**Simon Mead** @smead2 · Jul 29, 2023 ...

There are good reasons and some data to suggest benefits will continue (and even grow, but opinions differ). Look to what happened in other incurable diseases now transformed long term eg MS. Clinical trials can't provide all the answers - crucial ones for sure - not 5yr outcome

2

537



**Jan** @810964733763B ...

These are happening now Greg for sure, and data from earlier, and formulations, and related mAb predicted to have fewer side

Relevant people



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This Post was deleted by the Post author. [Learn more](#)**Simon Mead** @smead2 · Jul 29, 2023

These are happening now Greg for sure, and data from earlier, and sc formulations, and related mAbs predicted to have fewer side effects, and combination treatment, and treating people at-high risk. There is an avalanche of data on its way over coming years.

2



1

553

**Simon Mead** @smead2 · Jul 29, 2023

I worry you put forward an argument for wait and see for these 5yr outcomes and massive further investment in drug development. However such a policy imo would freeze investment in the sector and inspire only nihilism. Not what i want to see and not an alternative to "false hope"

2



1

440

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Yes, my critique is HOW we enact change in research b4 policymaking. Disclaimer- self promotion:

1) promote prudent language abt treatments:  
[twitter.com/PhilAlz/status...](https://twitter.com/PhilAlz/status...)

2) criticize over-reliance on amyloid-lowering + 3) put forward testable alternatives:

**Timothy Daly, PhD** @PhilAlz · Feb 22, 2023

1/5 with @AlbertoEspay & @KarlHerrup in @ELSNeurology Handb Clin Neurol Ch. 10 we argue research into neurodegeneration has not followed Popper's a priori "conjectures and refutations." Saving the amyloid hyp has meant: post hoc modifications...

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2



4

6.5K

This Post was deleted by the Post author. [Learn more](#)This Post was deleted by the Post author. [Learn more](#)This Post was deleted by the Post author. [Learn more](#)This Post was deleted by the Post author. [Learn more](#)**Jan**  
@810964733763B

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@Adrian\_H

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**Simon Mead** @smead2 · Jul 29, 2023

You make fair points here and I have called out hype in the UK at times. On the other I feel the risks are exaggerated by some in the context of disease severity and claims of meaningless treatment effects just as misleading as the hype

2 6 769

**Ryan Townley** @DrTFromKC · Jul 29, 2023

Same.

Anti-amyloid salesmen to the left of me and anti-anti-amyloid deniers to the right of me...

Stuck in the middle wanting longer term data in more generalizable populations and at even earlier stages of disease...

2 9 634

**Timothy Daly, PhD** @PhilAiz · Jul 29, 2023

"Salesmen" and "deniers" seems a little harsh as rhetorical portraits of intellectual differences go. Do enlighten us as to the virtuous posture to adopt ;). I see no problem with staying patient-focused, data-driven, and critical of precocious claims, allowing for disagreement.

1 3 570

**Ryan Townley** @DrTFromKC · Jul 29, 2023

There are clearly both portrayed in this thread.

If you don't consider yourself one of those, then great! We can be in the middle together.

1 2 620

**Timothy Daly, PhD** @PhilAiz · Jul 29, 2023

It is not whether I consider myself one or not (and who would, really?!), but whether my beliefs and actions here and elsewhere reflect intellectual laziness and "partisan" behaviour. I respect your stance, as you know

2 608

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**Jan**  
@810964733763B**Andrew Lees** @ajlees · Jul 29, 2023

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This Post was deleted by the Post author. [Learn more](#)**Andrew Lees** @ajlees · Jul 29, 2023

For me that is one of the most disappointing aspects of this sad charade. They are behaving like a new arm of the medical industrial complex

1



7

655

**Ash Paul** @pash22 · Jul 29, 2023

What do you mean by 'new arm ... ' Andrew. The phrase 'new M-I-C' was invented by the legendary Prof [#AndrewReIman](#) in 1980 and I'm not sure it has ever had a premature demise since then.

1



1

631

**Andrew Lees** @ajlees · Jul 29, 2023

Perhaps additional arm would have been a better way to express it

1



2

707

**Dan Clinton - The Awesome Nursing** @DanClintc · Jul 29, 2023

More PET scans, more MRIs, more infusions, more false hope, more screening, more death, more customers, more who had 7 yrs to advanced dementia now in nursing homes with MMSE of 4 s/p ARIA, more cerebral edema, more macrohemorrhage. 0 patients improved. 0 disease process halted.

1

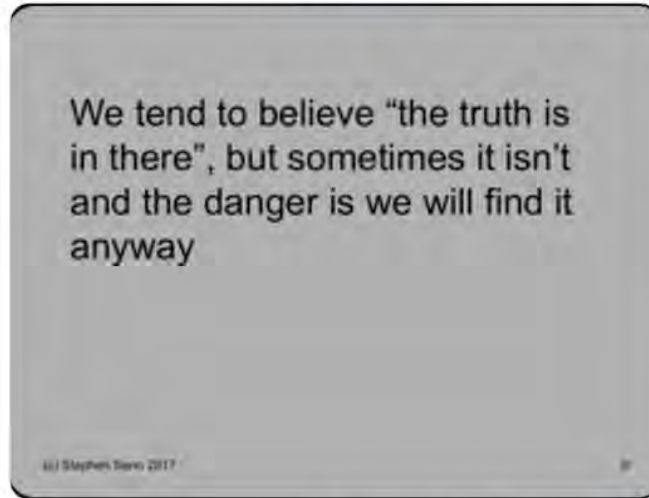


1

670

**Ash Paul** @pash22 · Jul 30, 2023

While I'm not so pessimistic and do hope/pray that genuine researchers like Nicolas, Ryan & Simon et al will come up with the right answers one day, I'm always reminded of the salutary warning given by the redoubtable Prof [@stephensenn](#), way back in 2017



1



4

820

**Dan Clinton - The Awesome Nursing** @DanClintc · Jul 30, 2023

After 20 yrs of amyloid removal failing to improve cognition Alzheimer's researchers have now lowered the bar to claim any slowed descent meaningful. What was insignificant b4 is now meaningful. What was unsafe before is now desperately rationalized. Harm & failure r inevitable

1



2

797

**Dan Clinton - The Awesome Nursing** @DanClintc · Jul 30, 2023

Giving a noncurative therapy that has a 1.5% absolute risk of death, permanent brain damage, or anaphylaxis because the 622 out of 853 who best tolerated donanemab slowed 7% vs 9% is an act of

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**Jan** @810964733763B

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Dan Clinton - The Awesome Nursing

@DanClintonRN · Jul 30, 2023

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Pre-diabetes: can prevention come too soon? - Evidently Cochrane

From evidentlycochrane.net

Andrew Lees @ajlees · Aug 8, 2023

Over here even some diabetes consultants reject prediabetes

1 1 1 663

David Jones @DavidJonesBrain · Aug 8, 2023

Do you reject MGUS?

2 1 476

Ash Paul @pash22 · Aug 8, 2023

A person who has lived with MGUS for 1 year has about a 1% risk of developing multiple myeloma. I could be wrong @ManniMD1 @AaronGoodman33

3 1 486

David Jones @DavidJonesBrain · Aug 8, 2023

If I had MGUS I would be glad that my doctor had the medical knowledge about the condition to tell me this. Ignoring it would not have lead to the development of that medical knowledge.

1 447

Lon S. Schneider, MD @LonSchneiderMD · Aug 8, 2023

Exactly, so when and under what conditions does a measurement of an amyloid become interpretable as high and/or an -opathy, ie, a sickness?

2 480

David Jones @DavidJonesBrain · Aug 8, 2023

This is an operational question. Let's define the thing we are operationalizing first.

1 1 481

Ash Paul @pash22 · Aug 8, 2023

Prob is the enthusiasts of early SMM Rx r jumpng in 2 Rx SMM whereas the anti early Rx grup say we do not yet have a consensus defntn of high-risk SMM, we have not identified optimal Rx strategy 4 these pts & we only have conflicting data from phase III studies. Sounds familiar?

1 484

David Jones @DavidJonesBrain · Aug 8, 2023

If you want to develop a knowledge base, then you need an agreed upon ontology. We all openly discuss preclinical beta-amyloid positive biological states and this will occur in clinical practice. Ignoring ontological facts is not a rational epistemic project.

1 1 513

Timothy Daly, PhD @PhilAlz · Aug 8, 2023

People who accept the biological definition of AD "openly discuss preclinical beta-amyloid positive biological states," those who don't tend to criticise it and prefer a vocab of risk, and besides, yours is not actually an argument for its integration into clinical practice.

1 1 593

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People who accept the biological basis of the "preclinical beta-amyloid positive biological states," those who don't tend to criticise it and prefer a vocab of risk, and besides, yours is not actually an argument for its integration into clinical practice.

David Jones @DavidJonesBrain · Aug 8, 2023

I understand that you don't like the reality, but that doesn't make it unreal. I will be seeing patients that are in this biological state and I will need to have a medical knowledge base to inform the medical care I provide them.

4 3 704

Andrew Lees @ajlees · Aug 8, 2023

You will blind them with science and perhaps unintentionally frighten them with the results of unnecessary tests or have i misunderstood your treatment approach?

4 2 1.5K

Ash Paul @pash22 · Aug 17, 2023

Madhav @MadhavThambiset 's comments on a recent Alz' article by @writergina

Madhav Thambisetty @MadhavThambiset · Aug 17, 2023

tinyurl.com/yc2usd6d "Are outcomes worse in those with symptomatic ARIA compared to those without symptoms? Are they worse in those with severe symptoms? These results have not been published for either lecanemab or aducanumab to date." @pash22 @ProfRobHoward @gregggonssalves

1 1 1.5K

Ash Paul @pash22 · Aug 19, 2023

Very pertinent tweet by Eric @EWidera

Eric Widera, MD @EWidera · Aug 17, 2023

When did the @NIHaging get in the business of writing clinical guidelines & why are they writing one with the @alzassociation where a 7 of 22 committee members are from industry? Read @AmerGeriatrics feedback on NIA-AA Clinical Guideliens for Alzheimers: [americangeriatrics.org/sites/default/](https://americangeriatrics.org/sites/default/)...

1 4 1.4K

Ash Paul @pash22 · Aug 22, 2023

New treatments for Alzheimer's disease: Blazing trails or the road to nowhere? [bmj.com/content/382/bm...](https://bmj.com/content/382/bm...) via @ProfRobHoward et al



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Adrian H @Adrian\_H

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1.8K

Ash Paul

@pash22

Aug 22, 2023

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Eligibility for Anti-Amyloid Treatment in a Population-Based Study of Cognitive Aging [n.neurology.org/content/early/...](https://www.neurology.org/content/early/2023/08/21/NEUR-2023-0411) via [@vijaykramanan](#) et al

Neurology

neurology.org

Eligibility for Anti-Amyloid Treatment in a Popula

Background and ObjectivesTreatment options

for Alzheimer disease (AD) are limited and ha...

1

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2

2.7K

Lon S. Schneider, MD

@LonSchneiderMD

Aug 22, 2023

...

Opportunity to say again:  
People eligible for anti-amyloid antibodies are minimally/mildly memory-impaired, generally healthy with few medical issues, largely self-sufficient & social.  
Most important, they retain capacity to make decisions & give informed consent for treatment.

1

1

5

957

Ash Paul

@pash22

Aug 24, 2023

...

Lecanemab: Looking before we leap

Madhav Thambisetty

@MadhavThambiset

Aug 24, 2023

...

Lecanemab: Looking Before We Leap  
"Before adopting lecanemab, we need to know that lecanemab isn't less effective, vastly more harmful, and 100x more costly than donepezil."  
[n.neurology.org/content/early/...](https://www.neurology.org/content/early/2023/08/21/NEUR-2023-0411) @ProfRobHoward @pash22 ...  
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1

4

1K

Ash Paul

@pash22

Aug 25, 2023

...

[@MelisAnaturk](#) et al dementia risk study finds 11 key factors behind condition: Predictive tool 'significantly outperforms' others available and could help avert about 40% of cases  
[theguardian.com/society/2023/a...](https://www.theguardian.com/society/2023/aug/25/dementia-risk-study) via [@andrewgregory](#) Most prediction tools are rubbish according to ... 1/n

theguardian.com

Dementia risk study finds 11 key factors behind

Predictive tool 'significantly outperforms' others

available and could help avert about 40% of ...

2

2

532

Ash Paul

@pash22

Aug 25, 2023

...

2/n ... the world's leading researchers [@GSCollins](#) & [@MaartenvSmeden](#) & [@laure\\_wynants](#) . No idea how good this prediction tool is!

1

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1 244

Ash Paul @pash22 · Aug 25, 2023

3/n ... Here's the full study [📄](#)

"Development and validation of a dementia risk score in the UK Biobank and Whitehall II cohorts"


mentalhealth.bmj.com

Development and validation of a dementia risk score in the UK Biobank and Whitehall II cohorts. Background Current dementia risk scores have had limited success in consistently identifying...

1 307

Ash Paul @pash22 · Aug 31, 2023

New Alzheimer's drugs don't deserve the hype: here's why [theconversation.com/new-alzheimers...](https://theconversation.com/new-alzheimers-drugs-dont-deserve-the-hype-here-s-why) via @seb\_walsh



New Alzheimer's drugs don't deserve the hype – here's why

From theconversation.com

3 367

Ash Paul @pash22 · Sep 3, 2023

Amyloid-related imaging abnormalities (ARIA): radiological, biological and clinical characteristics [academic.oup.com/brain/advance...](https://academic.oup.com/brain/advance-article-abstract/doi/10.1093/brain/awz400/5581111) via @ApostolovaLiana et al

Madhav Thambisetty @MadhavThambiset

· Sep 3, 2023

@ProfRobHoward @nvillain\_alz @pash22 @LonSchneiderMD @geoperry @KarlHerrup @kathy\_y\_liu @SFAckley @VincentPlanche @gregggonsalves @reshmagar @jsross119 x.com/MadhavThambise...

2 719

Timothy Daly, PhD @PhilAlz · Oct 11, 2023

May interest members of this thread:

Timothy Daly, PhD @PhilAlz · Oct 11, 2023

The @bmj\_latest just published my letter "Informing consent to antibodies in Alzheimer's disease"

in response to @ProfRobHoward.

... [Show more](#)

1 621

Andrew Lees @ajlees · Oct 11, 2023

The problem is that desperate people are rarely rational Do you think it would be ethical for a physician to refuse to offer and supervise this treatment when working in the public health system?

Jan @810964733763B

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Andrew Lees @ajlees · Oct 11, 2023

The problem is that desperate people are rarely rational  
Do you think it would be ethical for a physician to refuse to offer and supervise this treatment when working in the public health system?

1 5 315

Robert Howard @ProfRobHoward · Oct 11, 2023

In England, we can look to NICE to make an informed and fair judgement about whether these drugs offer worthwhile benefits to patients and are cost-effective within the NHS. I'll go with whatever they decide.

2 4 495

Lon S. Schneider, MD @LonSchneiderMD · Oct 11, 2023

Must be a British thing. Antibodies are available & sold in the US based on evidence that at least 1 person might benefit & mainly on the hope that benefits might grow over time.  
FDA approval makes it an ordinary medical wager: "You pays your nickel and you takes your chances"

2 1 8 844

Nicolas Villain @nvillain\_alz · Oct 11, 2023

You're the "land of hope"! We, whining conservative Europeans, are always one step behind: we sacrifice innovation on the altar of public service and public health!

1 4 272

Ash Paul @pash22 · Oct 11, 2023

How do you define innovation? Innovation & invention are as different as chalk and cheese. Invention is something new whereas innovation is something new that ALWAYS adds VALUE.

1 227

Nicolas Villain @nvillain\_alz · Oct 11, 2023

Don't worry, Ash: you are facing a French leftist who chose a public service academic career when the French Healthcare system isn't in top form and when salary differences have never been so high between the public and private systems 😊 Still, I admit that the US innovate more

1 2 221

Ash Paul @pash22 · Oct 11, 2023

Hi Nicolas, the most innovative country in the world, taking into account everything, is your neighbour

Global Innovation Index 2022

Below, we show the most innovative countries in the world, based on analysis from the WIPO Global Innovation Index.

Scores are based on the following 7 categories:

- Business Sophistication
- Human Capital & Research
- Infrastructure
- Institutions
- Market Sophistication
- Knowledge and Technology Capabilities
- Creative Output

For the 12th year in a row, Switzerland leads the world in its high number of patents and institutional strength.

TOP 10 COUNTRIES:

- 1. Switzerland
- 2. United States
- 3. Sweden
- 4. United Kingdom
- 5. Denmark
- 6. Netherlands
- 7. Korea
- 8. France
- 9. Germany
- 10. Japan

Relevant people

Adrian H @Adrian\_H

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Je ne te parle pas, je chante pour moi-même, je chante pour moi-même! Et je pense! il n'est pas défendu de penser! I don't like bullies. I block anon idiots.

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- Nicolas Villain @nvillain\_alz · Oct 11, 2023

Thx, Ash! I didn't know that such an index existed! Still, my sentence is correct: "The US innovate more" (than France and the UK), according to your doc, right?

PS: public healthcare in Switzerland isn't a thing either...
- Jason Cohen @MemoryDoc · Oct 11, 2023

I can answer for my entire country: We would rather pay more and die younger with no regard for our neighbors or public health if there is even a small chance we can "get ahead"
- David Jones @DavidJonesBrain · Oct 12, 2023

There are different virtues in every perspective. I have seen miracles that would only occur in certain circumstances. That may not matter to populations, but it did to the individuals who experienced the miracle. Those events can teach us how to scale to everyone.
- Ash Paul @pash22 · Oct 12, 2023

You are living in cloud cuckooland David IMO. Because you deal with such a niche disease like iNPH, your perspective on scaling up stuff for the good of everyone is warped. This scaling up, that you talk abt so passionately, is not going to happen in ur lifetime ... 1/n
- Ash Paul @pash22 · Oct 12, 2023

2/n ... your children's lifetime, your grandchildren's lifetime or even in your great grandchildren's lifetime. Have you read the latest @SenateFloor report?  
[mobidrive.com/sharelink/p/cG...](https://mobidrive.com/sharelink/p/cG...)

United States Senate  
HEALTH, EDUCATION, LABOR, AND PENSIONS COMMITTEE  
Bernard Sanders, Chair  
Majority Staff Report  
October 10, 2023

Executive Charity  
Major Non-Profit Hospitals Take Advantage of Tax Breaks and Prioritize CEO Pay Over Helping Patients Afford Medical Care

Introduction

In 2007, Carrie Barrett needed a heart catheterization after experiencing chest pain and shortness of breath. She went to a Methodist Le Bonheur ("Methodist") hospital in Memphis, Tennessee, and walked out with the needed procedure completed and a \$12,019 bill for her medical stay. Ms. Barrett made less than \$12 an hour and had no hope of paying back that bill. But the hospital not only refused to help Barrett afford her bill, it instead piled on interest and sent the bill to collections. By June 2019, Ms. Barrett owed over \$13,000, nearly three times the original cost of the procedure and more than twice what she earned in a year.

Stories like Ms. Barrett's are far too common. But they are even more egregious when the hospital is a non-profit that is required to be "organized and operated exclusively for charitable purposes." Nearly half of American hospitals are non-profits, a status that affords them an incredible benefit: exemption from federal, state, and local taxation. In 2020, the nation's 2,978 non-profit hospitals received an estimated \$28 billion in federal, state, and local tax benefits as a result of not paying those taxes—an average of \$9.4 million per hospital. One study also found that tax breaks accounted for 44 percent of non-profit hospitals' net income in that same year.

In return for the tax benefits, the federal government requires these hospitals to operate for the public benefit by providing a set of community benefits, which includes ensuring low-income individuals receive medical care for free or at significantly reduced rates—a practice known as "charity care." The Patient Protection and Affordable Care Act (commonly known as the ACA) added additional community benefit requirements, including stipulating that hospitals must maintain a publicly available financial assistance program and prohibiting hospitals from taking "extraordinary collection activities" against patients who are eligible for charity care, such as selling a patient's debt to a third party, placing a lien on a patient's property, or starting other legal proceedings against the patient.

As Ms. Barrett's case shows, hospitals have gladly accepted the tax benefits that come with non-profit status but have failed to provide the required community benefits. Non-profit hospitals spent only an estimated \$16 billion on charity care in 2020, or about 57 percent of the value of their tax breaks in the same year. Those hospitals have made information about their charity care programs difficult to access, leaving many patients unaware that they may qualify for these

Relevant people

- Adrian H  
@Adrian\_H

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- Dan Clinton - The Av  
@DanClintonRN

Nurse, Tutor, Author. Believer in good definitions, the scientific method, & comparing benefits & harms in like terms. Seeking to prevent iatrogenic harm.
- Ash Paul  
@pash22

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“charity care.” The Patient Protection and Affordable Care Act (commonly known as the ACA) added additional community benefit requirements, including stipulating that hospitals must maintain a publicly available financial assistance program and prohibiting hospitals from taking “extraordinary collection actions” against patients who are eligible for charity care, such as selling a patient’s debt to a third party, placing a lien on a patient’s property, or starting other legal proceedings against the patient.”

As Ms. Barrett’s case shows, hospitals have gladly accepted the tax benefits that come with non-profit status but have failed to provide the required community benefits. Non-profit hospitals spend only an estimated \$16 billion on charity care in 2020, or about 5% percent of the value of their tax breaks in the same year.<sup>10</sup> Those hospitals have made information about their charity care programs difficult to access, leaving many patients unaware that they may qualify for free or discounted care.<sup>11</sup> Some hospitals also aggressively try to collect from patients through practices that verge on extraordinary collection practices. One recent study found that in 2013, non-profit

1

291

**LogarithmicDis** @LogarithmicDis · Oct 12, 2023

...

Ash, I think you misunderstood what @DavidJonesBrain was saying.

Nevertheless, no reason to be insulting. Massive respect to him and @NaipMayo

2

4

233

**Nick Corriveau-Lecavalier, PhD** @CorriveauNick · Oct 12, 2023

...

Rare and atypical diseases exist and are underestimated, are often misdiagnosed, and patients suffer. Such thinking leads nowhere and hurt patients.

Argue and insult all you want. We'll be busy helping these people.

1

1


8

280

**Ash Paul** @pash22 · Oct 12, 2023

...

Hi Nick, I'm expressing my views as a clinical payer. There is plenty of evidence to suggest that rare diseases should not get special treatment from clinical payers eg [jme.bmj.com/content/48/2/86](https://jme.bmj.com/content/48/2/86) via @monicaqfm



From [jme.bmj.com](https://jme.bmj.com)

2

235

**Nick Corriveau-Lecavalier, PhD** @CorriveauNick · Oct 12, 2023

...

Some of these diseases are more frequent than you want to think. I agree that bigger problems require bigger commitments. But your comments about patients suffering from these diseases & clinician-researchers helping these patients are at times frankly insensitive and demeaning.

2

1

222

**LogarithmicDis** @LogarithmicDis · Oct 12, 2023

...

Remember when Sjögren’s was thought to be rare? Now quite common.

Funneling patients in and out of standard care for only commonly diagnosed diseases is not payer prudent or clinically ethical.

1

2

196

**Ash Paul** @pash22 · Oct 12, 2023

...

My job as a clinical payer in a finitely funded and publicly funded hithcare system is unambiguously and crystal clear. For the fixed amount of ££ that Parliament gives us yearly. we need to spend that

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Ash Paul

@pash22 · Oct 12, 2023

My job as a clinical payer in a finitely funded and publicly funded hlticare system is unambiguously and crystal clear. For the fixed amount of ££ that Parliament gives us yearly, we need to spend that wisely to ensure healthgain for our local population ... 1/n

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202

Nicolas Villain

@nvillain\_alz · Oct 12, 2023

If I may... You both sound very knowledgeable in your areas of expertise with very different perspectives. I'm like Dave, an expert physician from a tertiary center whose added value is to make complex diagnoses. Thus, we face daily situations where we recognize the

1/3

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195

Nicolas Villain

@nvillain\_alz · Oct 12, 2023

current limitations of medical training, guidelines, etc., and can propose a clear vision of how adaptation of this training and guidelines could be both helpful to patients and cost effective. We also deal with common diseases (iNPH isn't rare, Ash), unlike some specialists

2/3

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206

Nicolas Villain

@nvillain\_alz · Oct 12, 2023

in other fields. I think we could all be winners if we could improve the dialogues between us: the global group economic perspective with its pragmatic and framework limitations and the specialist with an individual perspective that enlightens and proposes original solutions.

3/3

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579

Nicolas Villain

@nvillain\_alz · Oct 12, 2023

PS: is it just me, or do some escort bots target our thread??

4

2

303

Madhav Thambisetty

@MadhavThambiset · Oct 12, 2023

Just you my friend. Its the price you pay for your dashing good looks, magnetic personality and incandescent intellect.

1

5

218

Nicolas Villain

@nvillain\_alz · Oct 12, 2023

That was my first guess indeed 🤔🤔🤔🤔

1

3

214

LogarithmicDis

@LogarithmicDis · Oct 12, 2023

Et être français aussi 🤔 toujours vrai, il semble, Nic!

1

186

Nicolas Villain

@nvillain\_alz · Oct 12, 2023

Jan

@810964733763B

...

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@Adrian\_H

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1 2 222

**Lon S. Schneider, MD** @LonSchneiderMD · Oct 12, 2023  
This is more like it 😊



2 3 221

**Ash Paul** @pash22 · Oct 12, 2023  
How about this one Lon? Makes Nicolas look more like a DSME secret service agent doesn't it?



**Jan**  
@810964733763B

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@Adrian\_H Follow

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211

Lon S. Schneider, MD

@LonSchneiderMD · Oct 12, 2023

Not really, looks like someone who still has all his toes.

1

1

218

Madhav Thambisetty

@MadhavThambiset · Oct 12, 2023

You can tell he speaks softly and carries a big reflex hammer

1

4

247

Nicolas Villain

@nvillain\_alz · Oct 12, 2023

French style Reflex hammer: not the big Queen Square model, but rather Babinski's ;)

2

2

332

Trey Bateman

@RenegadeSynapse · Oct 12, 2023

Oh, good, this thread has moved onto something less controversial among neurologists, like reflex hammer choice 🤔

3

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267

Madhav Thambisetty

@MadhavThambiset · Oct 12, 2023

I fear Rob will now feel obliged to share candid pictures of his CBT manual

2

5

296

Lon S. Schneider, MD

@LonSchneiderMD · Oct 12, 2023

Mostly he'll show you the effect size for cbt in prodromal AD and how it dwarfs lecanemab's. Which of course isn't saying much.

2

6

321

LogarithmicDis

@LogarithmicDis · Oct 12, 2023

the subject of ongoing federal probes, has suffered another blow. A much-anticipated investigation by the City University of New York has accused neuroscientist Hoau-Yan Wang, a CUNY faculty member and longtime Cassava collaborator, of scientific misconduct involving 20 research papers. Many provided key support for simufilam's jump from the lab into ongoing clinical trials.

The investigative committee found numerous signs that images were improperly manipulated, for example in a 2012 paper in *The Journal of Neuroscience* that suggested simufilam can blunt the

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The investigative committee found numerous signs that images were improperly manipulated, for example in a 2012 paper in *The Journal of Neuroscience* that suggested simufilam can blunt the pathological effects of beta amyloid, a protein widely thought to drive Alzheimer's disease. It also concluded that Lindsay Burns, Cassava's senior vice president for neuroscience and a co-author on several of...

2 2 258


**Lon S. Schneider, MD** @LonSchneiderMD · Oct 12, 2023  
Let's see how long it takes for NIH and OSI to act. It will be fun to see who Cassava's antisemitic trolls go after.

3 1 5 456

**LogarithmicDis** @LogarithmicDis · Oct 13, 2023  
Lon et al, would you trust the guy hammered by his own university committee for egregious misconduct (and reported to @HHS\_ORI ) to continue producing the laboratory endpoints for ongoing clinical trials?

Madness.

Hello @FDACDERDirector




Co-developer of Cassava's potential Alzheimer's drug cited for 'egregio...

From science.org

1 267

**Ash Paul** @pash22 · Oct 13, 2023  
@CassavaSciences responds to @CUNY accusations of 'scientific misconduct,' reiterates support of data behind controversial Alzheimer's drug endpts.com/cassava-scienc... via @KatherineMLewin @Adrian\_H @ClicksAndHisses



Cassava responds to accusations of 'scientific misconduct,' reiterates s...

From endpts.com

1 3 370

**Adrian H** @Adrian\_H · Oct 13, 2023

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**Adrian H**  
@Adrian\_H

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From endpts.com

1

3

370

Adrian H

@Adrian\_H · Oct 13, 2023

The investigation report made a finding of “egregious misconduct”— it’s no longer a mere accusation.

1

2

383

Robert Howard

@ProfRobHoward · Oct 13, 2023

But, only 20 papers were involved, Adrian.

1

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356

Ash Paul

@pash22 · Oct 13, 2023

That should keep @NIH & @HHS\_ORI busy presumably.

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335

Ash Paul

@pash22 · Oct 13, 2023

In addition, Adam @adamfeuerstein has made a very pertinent point on twitter [👉](#) [twitter.com/adamfeuerstein...](#) cc @FDACDERDirector

Adam Feuerstein

@adamfeuerstein · Oct 12, 2023

Replying to @adamfeuerstein

Forget the stock for a moment, the real tragedy of \$SAVA and its abhorrent behavior with respect to the development of simufilam is that people with Alzheimer’s have been duped into enrolling in clinical trials that have no chance of succeeding.

3

4

873

Dan Clinton - The Awesome Nursin

@DanClint · Oct 13, 2023

Seems like selective outrage to only rail against \$SAVA and simufilam giving Alzheimer’s patients false hope when amyloid-removing antibodies are now proven not to work and proven to commonly cause serious brain damage.

2

4

297

Adrian H

@Adrian\_H

It’s a totally different issue, but I can assure you that many of those outraged with \$SAVA were also outraged with Aduhelm and FDA shenanigans and skeptical of amyloid Abs. But there’s equivalence between that and allegedly completely fake science and an allegedly imaginary drug

5:24 PM · Oct 13, 2023 · 749 Views

4

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3

Post your reply

Reply

Robert Howard

@ProfRobHoward · Oct 13, 2023

Although the Aduhelm shenanigans and Biogen’s behaviour ran pretty close.

4

208

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Jan

@810964733763B

...

Adrian H

@Adrian\_H · Oct 13, 2023

^no equivalence, obvs

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@Adrian\_H

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- Adrian H** @Adrian\_H · Oct 13, 2023  
^no equivalence, obv

1

93
- Dan Clinton - The Awesome Nursin** @DanClint · Oct 13, 2023  
I agree that there's a difference between making up results and misinterpreting results, but the issue of patients being "duped into enrolling in clinical trials that have no chance of succeeding," now applies to anti-amyloid antibodies.

2

1

243
- Adrian H** @Adrian\_H · Oct 13, 2023  
It's a tough call... some of the newer anti-amyloid antibodies clearly are doing \*something\*, though I agree the clinical value remains very questionable. But it seems reasonable to at least keep studying them.

2

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265
- Ash Paul** @pash22 · Oct 14, 2023  
Not sure what @alzassociation & @DrMariaALZ are upto though, as Madhav @MadhavThambiset has discovered

2

1

326
- Madhav Thambisetty** @MadhavThambiset · Oct 14, 2023  
Only 1 of these can be true. One is the FDA label for Amyvid, the 1st approved amyloid PET tracer. 2nd is the Alz Assoc's giddy response to CMS decision to cover it announced today @marcomeglio1 @LonSchneiderMD @ProfRobHoward @pash22 @geraldposner @RitaRubin @judith\_graham

1

2

181
- Lon S. Schneider, MD** @LonSchneiderMD · Oct 14, 2023  
Up to? The mission of #EndAlz is to make a market and increase donations from their grass roots supporters.

2

3

181
- Dan Clinton - The Awesome Nursin** @DanClint · Oct 14, 2023  
And, whether through intentional greed or profound idiocy, by changing the definition of Alzheimer's to only requiring the presence of amyloid the Alzheimer's association will make Alzheimer's literally incurable.

1

1

196
- Ash Paul** @pash22 · Oct 14, 2023  
Isn't curing for patients bad business?  
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